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Development of Integrated Platforms for Automated Kinetic Profiling of Chemical Reactions

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March 2024

A thesis submitted for the degree of Doctor of Philosophy

I, Eleni Grammenou, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

Date: __31/03/2024__

Abstract

Continuous flow micro- and milli-scale reactors, as an alternative to conventional batch reactors, offer several advantages in the study of chemical reactions. Characterised by enhanced heat and mass transfer rates, ease of automation for precise control of reaction conditions, and seamless integration with inline and online analytical tools, miniaturised systems facilitate rapid acquisition of kinetic data, crucial for process scale-up. This thesis describes the development of automated platforms designed for the systematic acquisition of kinetic information for both heterogeneous and homogeneous systems. The core of this research involves the fabrication and utilisation of miniaturised reactors, readily integrated into experimental setups that are coupled with chromatographic and spectroscopic techniques. An automated open loop microreactor platform was developed for the kinetic model discrimination and parameter estimation of the heterogeneously catalysed levulinic acid esterification to ethyl levulinate. This reaction was conducted in a Single Pellet String Reactor and the associated hydrodynamics and liquid-to-solid external mass transfer process were numerically investigated at macroscopic and microscopic scales. Different aspect ratios were simulated that yielded empirical correlations for mass transfer in these systems, enhancing the understanding of the reaction dynamics. The potential of coupling non-invasive spectroscopy with continuous systems for real-time reaction monitoring and fast kinetic data acquisition were exemplified via the fabrication of a miniaturised CSTR unit integrated with a cooling/heating system, equipped with an inline Raman spectrometer probe. Its mixing characteristics were thoroughly investigated through both experimental and computational approaches and the efficacy to produce fast steady-state kinetic data, acting both as a reactor and a stirred flowcell, was shown for an imine synthesis reaction in an automated experimental platform. To further demonstrate the efficiency of the system, the same reaction was tested in intuitively designed transient experiments of single and multi-variable ramps, which dramatically reduced the experimental time required and led to higher precision in the parameter estimation.

Impact statement

In recent years, there has been a growing interest in automating and miniaturising experimental setups for kinetic studies using continuous-flow chemistry [1]. Automation offers several advantages, including improved reproducibility, precise control over experimental parameters, and increased throughput [2], whilst miniaturisation enables researchers to explore reaction kinetics in wide operating process windows [3-5], with reduced waste generation, compared to traditional testing methods [6, 7]. With the proliferation of continuous-flow kinetic applications comes a parallel increase in novel methodologies for efficient kinetic analysis, which expand to include the integration of inline process analytical tools (PAT) [8], as well as single [9] and multi-variable [10] manipulation methods that deviate from conventional steady state sampling. When combined, these approaches can generate a full kinetic profile within a reduced timeframe.

The work presented in this thesis focuses on leveraging automation, online/inline analysis, miniaturisation and transient experimentation to propel advancements in the realm of chemical kinetics. By incorporating these four elements, the study endeavours to enhance the efficiency of acquiring kinetic data and identifying reliable models for liquid-phase catalytic and non-catalytic chemical reactions.

Highlights:

Initially, flow patterns and liquid-to-particle mass transfer in cylindrical Single Pellet String Reactors (SPSRs) with aspect ratios ranging from 1.06 to 1.68 were comprehensively investigated. Using COMSOL Multiphysics® 6.1, a validated model was developed and extended to cover Reynolds numbers up to 100. By comparing two approaches - a macroscopic method based on Residence Time Distribution (RTD) studies and used for conventional packed beds, and a microscopic method utilising local mass flux calculations - it was revealed that the macroscopic treatment overestimated mass transfer in reactors with small aspect ratios. Consequently, new correlations were established based on the microscopic approach to estimate the liquid-to-solid mass transfer coefficient, highlighting the influence of aspect ratio on enhancing mass transfer. This work presented an efficient alternative to labour-intensive experimental procedures for estimating mass transfer coefficients in SPSRs and received recognition with two 1st place poster awards: UK Catalysis Fundamentals and Practice Summer School (July 2022), and Rideal Conference 2023 (May 2023).

A SPSR of 1.25 aspect ratio was used as part of an automated platform coupled with online High Performance Liquid Chromatography (HPLC), developed using LabVIEW, to conduct

pre-planned experiments for the identification of a kinetic model for the esterification of levulinic acid and ethanol over heterogeneous Amberlyst-15 catalyst. The reaction is of industrial importance as ethyl levulinate, the product of the esterification, exhibits good compatibility with most gasoline blends. An extensive library of power law, Langmuir-Hinshelwood-Hougen-Watson and Eley-Rideal models was screened through the application of a general procedure for model discrimination and parameter estimation. The procedure was applied for the investigation of different design spaces and allowed for the reformulation of models to include temperature-dependent parameters, the former leading to an increase in model identifiability and the latter resulting to enhanced model fitting. Two suitable kinetic models out of twenty-eight candidates, a Langmuir-Hinshelwood-Hougen-Watson and an Eley-Rideal model, were identified both of which accounted for the adsorption of water on Amberlyst-15.

A second reactor design, a temperature-controlled miniaturised CSTR (m-CSTR) equipped with a custom-made impeller, was fabricated and automated using LabVIEW, enabling real-time acquisition of reaction kinetics through inline Raman spectroscopy. Investigation of the m-CSTR's mixing behaviour, both experimentally and computationally, showcased its optimal performance and superior micromixing capabilities compared to conventional stirring bars, along with providing operational guidelines. Kinetic parameters for the synthesis of *n*-benzylidenebenzylamine were derived using Raman spectral data directly from within the reactor, processed with a simple yet effective baseline correction method. The reactor's versatility can extend to monitoring reactions involving solid formation or heterogeneous catalysts, rendering it a valuable tool for efficient kinetic data acquisition. This work was recognized at the 27th International Symposium for Chemical Reaction Engineering (June 2023), where it received the 1st place poster award from the Reaction Chemistry & Engineering Journal.

The extension of an automated reactor platform featuring the m-CSTR and inline Raman spectrometer for conducting transient experiment was also investigated. These transient experiments yielded kinetic parameters consistent with steady-state experiments, showcasing the efficiency of transient methods, particularly when coupled with non-invasive spectroscopic techniques and revealed limitations in experimental design, emphasizing the need for careful consideration in designing experiments to avoid low-information outcomes. These valuable insights provide guidance on optimising experimental strategies to efficiently estimate kinetic parameters, marking the first exploration of dynamic operation of milliscale CSTRs.

Acknowledgements

While I always thought the acknowledgement section should be kept formal, it would be disingenuous to stifle the personality that comes through in this part of the thesis. This PhD journey, from its inception to its completion, owes its success (and, let's be honest, its manageability) to the invaluable contributions of some truly remarkable individuals.

First and foremost, I would like to express my deepest gratitude to my primary supervisor, Prof. Asterios Gavriilidis, who has been an exceptional mentor. Professor, thank you for believing in me during moments of self-doubt and for consistently offering invaluable feedback on my work. Your regular check-ins on the progress of this PhD were not only a source of guidance but also provided the perfect forum to tackle challenges and generate new ideas.

I extend a massive thank you to my second supervisor, Prof. Federico Galvanin. Federico, aside from guiding me through the statistical aspects of this work, your positive personality and outlook on life have been a constant source of inspiration. Your support extended beyond research; during challenging times, your office door was always open, offering a listening ear and providing me with invaluable career advice when I faced setbacks. For this, and for all the times you reminded me that life extends beyond a LabVIEW computer screen and a setup in Lab 215, I am forever indebted.

I want to give a special thanks to Simon Dawes, the CAD and CNC milling expert, for assisting me with the reactor design and fabrication, for stepping in to help when everything seemed to be falling apart, and for patiently entertaining all my wild ideas with expertise. And to Nicholas Snead, the LabVIEW maestro, whose witty banter in the lab and knack for bringing my ideas to life were invaluable. For their mentorship in all things IR, I am deeply grateful to Martyn Towner and the late Prof. Paul McMillan from the Department of Chemistry at UCL.

A big shoutout to my friends and colleagues of the AG group for tolerating my loud voice (which could be notoriously heard from the IT room even when 305 door was closed) and quirky antics. To Suneha, Mabel and Dionysia; your contagious energy and daily check-ins turned the lab into a haven amidst the chaos of research life. I am immensely grateful to George, Solomon, Sayan and Jacopo for their invaluable feedback and support; sharing insights from your own work consistently enriched mine. A massive thank you, also, goes out to Dr. Maximilian Besenhard, who taught me more than just lab manners (like the time I broke my first pipette). Max, you've been a mentor and a friend, always there with a big smile and a word of comfort. Huge thanks to my collaborators, Andrea and Theresa, for handling every data-related request, big or small, with grace and efficiency.

There are a couple more people outside UCL that I would like to thank for their constant presence in my life. To my London friends - Aurora, Ekim, Inger, Oriol, Yavuz - thanks for the endless chats, fresh cardamom buns, Sunday strolls, career advice, warm hugs and postal cards that crossed oceans, all these little, yet ultimately significant, things that made life in London so much more enjoyable. And to my rock, Tris, you've been more than just a best friend; you've been a constant source of support, positivity, and nurturing love, through every personal and professional drama. From being my faithful Tuesday margarita companion at IOE, to maturing into (de)caffeinated queens at Bread by Bike and calling me out on my occasional paranoid behaviour, your presence has truly made all the difference.

To my Greek besties - Anastasia, Aris, Evi, Giorgos, Sophia - your friendship transcends geographical boundaries and has been a constant source of strength throughout my academic journey, from my days at NTUA to my time here at UCL. You've witnessed my evolution from a fresh MSc graduate to now eagerly awaiting your attendance at my graduation ceremony as a Dr. I'm forever grateful for the joy you bring to my life.

Lastly, I want to express my deepest gratitude to my family. To my beloved sister, Christina, although I regret not being more present in your life to celebrate your successes as appropriate, you have always provided love and support whenever I needed it. And to my dear yiayia, Eleni, your caring nature and missed presence over these four years fill my heart with warmth and longing. I promise to make more frequent visits to Athens now.

This thesis is dedicated to my parents, Hara and Giannis. Μαμά και μπαμπά, from the day you dropped me off at kindergarten, you have been my biggest supporters. In times of failure, you've been just a phone call away, offering a listening ear and a positive attitude to keep me going, even when my struggles sounded a bit 'Greek' to you. With every success, the warmth of your smile and the pride in your eyes amplified the celebration.

To conclude this acknowledgement section, I would like to share a poem by one of my favourite Greek poets, C. P. Cavafy. It serves as a reminder to continue pursuing my curiosity and to celebrate how far I've come. Ultimately, everything always works out in the end.

Σ' αυτές τες σκοτεινές κάμαρες, που περνώ
μέρες βαρυές, επάνω κάτω τριγυρνώ
για νάβρω τα παράθυρα.— Όταν ανοίξει
ένα παράθυρο θάναι παρηγορία.—
Μα τα παράθυρα δεν βρίσκονται, ή δεν μπορώ
να τάβρω. Και καλλίτερα ίσως να μην τα βρω.

Ίσως το φως θάναι μια νέα τυραννία.
Ποιος ξέρει τι καινούρια πράγματα θα δείξει.

Τα παράθυρα, Κ.Π. Καβάφης

In these dark rooms where I pass
such listless days, I wander up and down
looking for the windows – when a window opens
there will be some relief.

But there are no windows, or at least
I cannot find them. And perhaps it's just as well.
Perhaps the light would prove another torment.
Who knows what new things it would reveal.

The windows, C.P. Cavafy

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Nomenclature

Latin variables

A	Pre-exponential factor
A_0	Empty cross-section of the reactor channel
A_{int}	Cross-section of the reactor channel
a	Thermodynamic activity
Bo	Bodenstein number
b	Scaling factor
CI	Confidence interval
C_{W-P}	Weisz-Prater criterion
c	Concentration
c_b	Concentration in the bulk liquid
c_{BAI}	Concentration of benzaldehyde
c_{BAm}	Concentration of benzylamine
c_{BIm}	Concentration of <i>n</i> -benzylidenebenzylamine
c_{EL}	Concentration of ethyl levulinate
c_{EtOH}	Concentration of ethanol
c_{LA}	Concentration of levulinic acid
c_0	Inlet concentration
c_W	Concentration of water
c_s	Concentration on the catalyst surface
D	Reactor diameter
D_{ax}	Axial dispersion coefficient
D_e	Effective diffusivity
D_m	Molecular diffusion coefficient
D_s	Diameter of the stirrer
d_h	Hydraulic diameter
d_p	Particle diameter
$E(t)$	RTD curve (E-curve)
E_α	Energy of activation
F	F curve
f_w	Weighting factor
k_{LS}	External liquid-to-solid mass transfer coefficient
k	Kinetic rate constant
K	Adsorption constant
KP	Re-parameterised Arrhenius parameters
KP_{ads}	Re-parameterised Vant Hoff's parameters
L	Characteristic system length
$L_{reactor}$	Reactor length
$l_{optical}$	Optical path length within the measurement cell
MW	Molecular weight
m	Mass of catalyst
m_{A15}	Mass of Amberlyst-15 catalyst
N	Stirring frequency
N_{exp}	Number of experiments
N_u	Number of inputs/control variables
N_y	Number of responses
N_θ	Number of parameters

N_{particle}	Number of particles
N_{tanks}	Number of equally sized ideal CSTRs
n	Reaction order
P	Pressure
Pe	Peclet number
Q	Flowrate
Q_{initial}	Initial flowrate (baseline flowrate)
Q_0	Inlet flowrate
Re_h	Reynolds number based on the interstitial velocity and hydraulic diameter ($Re_h = \frac{\rho u_{\text{int}} d_h}{\mu_L}$)
Re_{int}	Reynolds number based on the interstitial velocity and particle diameter ($Re_{\text{int}} = \frac{\rho u_{\text{int}} d_p}{\mu_L}$)
Re_M	Reynolds number based on the diameter of the stirrer and the stirring speed ($Re_M = \frac{\rho N D_s^2}{\mu_L}$)
Re_0	Reynolds number based on the superficial velocity and particle diameter ($Re_0 = \frac{\rho u_0 d_p}{\mu_L}$)
r	Distance
r_p	Radius of particle
r'_{LA}	Rate of mass transfer of levulinic acid per mass of catalyst
S_w	Wall surface
S_p	Total surface of particles
Sc	Schmidt number
Sh	Sherwood number
T	Temperature
T_{initial}	Initial temperature (baseline temperature)
T_M	Reference temperature
T_0	Ambient temperature
t	Time
$\bar{t}$	Calculated mean residence time
t_i	Student's t-test value of each parameter i
t_m	Mixing time
u	Velocity
u_{int}	Interstitial velocity
u_0	Superficial velocity
V	Reactor volume
V_{molar}	Molar volume
V_p	Total volume of particles
X_s	Segregation index
x, y, z	Cartesian coordinates
Y	Ratio of acid mole number consumed by the redox reaction divided by the total acid mole number injected
Y_{ST}	Value of Y when the mixing process is infinitely slow

Greek variables

α	Total specific surface of the reactor bed
α_{acid}	Fraction of the acid solution volume added
α_Q	Flowrate ramp rate
α_T	Temperature ramp rate
α_V	Thermal expansion coefficient

Γ	Gamma function
γ	Activity coefficient
ΔH_i	Enthalpy of adsorption of i component
δ	Aspect ratio
δ_{film}	Thickness of boundary layer
ε	Reactor porosity
ε_p	Particle porosity
ε_{353}	Extinction coefficient at 353 nm
θ	Angle (Chapter 3)/Dimensionless residence time (Chapter 5)
λ	Tortuosity
μ	Ionic strength
μ_L	Dynamic viscosity
ρ	Fluid density
ρ_b	Bulk density of catalyst
ρ_c	Particle density
σ^2	Variance
σ_c	Constriction factor
τ	Theoretical residence time
φ_θ	Molar flux
χ^2	Chi square

Latin Vectors & Matrices

Navier-Stokes/Fick's law equations

F	External body forces
I	Unit vector
t	Tangential unit vector
u	Velocity

Design of experiments equations

C	Parameter correlation matrix
D	Design space
f	Vector of functions representing the state equation
g	Vector of functions representing the output equation
H	Hessian matrix
S	Sensitivity matrix
u	Inputs
V	Covariance matrix
x	State variables
y	System responses
$\hat{y}$	Model predicted system responses

Greek Vectors & Matrices

ε_i	Residuals
θ	Parameter
$\hat{\theta}$	Maximum Likelihood Estimates
τ	Viscous forces
φ	Design vector
Σ	Measurement error
ω	Angular velocity vector

Abbreviations

ANNs	Artificial Neural Networks
airPLS	Adaptive Iteratively Reweighted Penalized Least Squares methodology
ADM	Axial Dispersion Model
BPR	Back Pressure Regulator

CFD	Computational Fluid Dynamics
CSTR	Continuous Stirred-Tank Reactor
DoE	Design of Experiments
DL	Delay Loop
EL	Ethyl levulinate
ER	Eley-Rideal mechanism
EtOH	Ethanol
FC	Flowcell
(R)FIM	(Relative) Fisher Information Matrix
FR/EDM	Finite-Rate/Eddy Dissipation Model
FTIR	Fourier Transformed Infrared spectroscopy
GC	Gas Chromatography
HF/LF	High-Field/Low-Field
HP	Hotplate
HPLC	High Performance Liquid Chromatography
I.D.	Internal Diameter
IEM	Interaction by Exchange with the Mean model
LA	Levulinic acid
LHHW	Langmuir-Hinshelwood-Hougen-Watson mechanism
LHS	Latin Hypercube Sampling
LIF	Laser Induced Fluorescence
LS	Light source
MBDoE	Model Based Design of Experiments
MFC	Mass Flow Controller
MRF	Multiple Reference Frame
NMR	Nuclear Magnetic Resonance spectroscopy
OD	Optical Density
PFR	Plug Flow Reactor
PI	Pressure Indicator
PRV	Pressure Reducing Valve
PV	Pressure Vessel
RMSE	Root Mean Square Error
RTD	Residence Time Distribution
RV	(Pressure) Relief Valve
SM	Spectrometer
SNR	Signal to Noise Ratio
SP	Syringe Pump
SV	Switch Valve
SPSR	Single Pellet String Reactor
TIC	Temperature Indicator-Controller
TISM	Tanks-in-Series model
UHPLC	Ultrahigh Performance Liquid Chromatography
UV (vis)	Ultra-violet (visible) spectroscopy
V	Valve
W	Water
μSFS	Microfluidic stopped-flow system

Chapter 1. Introduction

1.1. Motivation and objectives

The inaugural quantitative study in chemical kinetics dates back in 1850, when Ferdinand Wilhelmy employed polarimetry to investigate the acid-catalysed conversion of sucrose into glucose and fructose in a batch reactor [11]. This landmark study marked the beginning of a journey to unravel the rates and mechanisms of chemical reactions, a pursuit indispensable across scientific and industrial domains, from pharmaceuticals [12] to petrochemicals [13]. The study of reaction kinetics equips scientists and engineers with tools to yield measurable impacts on chemical systems [14]. Reliable and robust kinetic models are crucial for designing reactors, understanding how reactions scale up from laboratory experiments to industrial settings, optimising process conditions to achieve maximum yield and selectivity, improving plant safety and offering mechanistic insights [15]. However, the development of kinetic models often proves a laborious task [16], as it involves identifying the most suitable kinetic model equations from a pool of candidate models, and then accurately estimating the model parameters, i.e. pre-exponential factors, activation energies and adsorption terms.

The advent of reaction automation represents a pivotal advancement, presenting safer and more efficient exploration of the chemical reaction space compared to traditional manual methods. The progress in developing fully or partially automated platforms has been propelled by the expansion of continuous flow small-scale reactors, which offer enhanced heat and mass transfer [17-21], reduced chemical consumption and facile integration with advanced analytical tools for real-time process monitoring. Automated reaction platforms integrate a variety of components for preparation of the reaction mixture, reactant displacement, reaction execution and workup, inline or online analytics and implementation of control software to orchestrate operations with minimal user supervision. This versatility supports a wide range of applications, including reaction discovery [22-24], reaction optimisation [25, 26] and reaction kinetics characterisation [9, 27-29].

In kinetic studies, researchers often collect time-series data under batch conditions, allowing for multiple time points to be obtained from a single experiment, followed by the formulation of a reaction model based on chemical intuition [30]. Kinetic profiling in flow systems offers several advantages, including precise and reproducible reagent addition control, accurate temperature and reaction time control, and the ability to explore challenging areas of design space that are impractical in a batch setting [31]. Despite the potential for improved control and reduced variability in reaction outcomes compared to batch vessels, designing platforms capable of exploring a broad range of chemical reaction space, allowing both steady-state and

transient experimentation, and facilitating plug-and-play functionality with minimal modifications can be complex and costly [32].

The aim of this thesis is to develop automated platforms for acquiring kinetic data and developing reliable kinetic models for heterogeneous catalytic and homogeneous non-catalytic reactions in liquid-phase systems. This is achieved through the synergy of automation, online/inline analysis, reactor miniaturisation, and systematic statistical analysis for model discrimination and precise parameter estimation. A key advancement lies in the flexibility of LabVIEW-controlled system to accommodate different reactor types and analytical techniques, while swiftly transitioning between experimental conditions with minor adjustments. Therefore, the objectives of this thesis can be summarised as follows:

- Fabrication of miniaturised reactors, with a special emphasis on relatively unexplored reactor concepts, such as Single Pellet String Reactors (SPSRs) and miniaturised Continuous Stirred Tank Reactors (m-CSTRs) and characterisation in terms of hydrodynamic behaviour, mixing and mass transfer, both experimentally and computationally, to be used for industrially relevant reactions. In this context, the kinetics of the heterogeneously catalysed synthesis of ethyl levulinate that is an emerging biofuel additive and the synthesis of *n*-benzylidenebenzylamine in methanol were studied.
- Integration of SPSRs and m-CSTRs with online High Performance Liquid Chromatography (HPLC) and inline Raman spectroscopy respectively, thereby expediting the process of reaction kinetics acquisition in both catalytic and non-catalytic liquid phase systems in automated platforms with minimal user intervention. Measurable goals are set for performance and operating characteristics of the automated platform, such as excellent reproducibility for all reactions studied: <5% standard deviation in the carbon balance, reaction temperatures ranging from 0 to 120 °C and operating pressures up to 6 barg.
- Expansion of the automated platform for fast kinetic data acquisition via transient experimentation coupled with Raman spectroscopy for precise parameter estimation and a richer mapping of the design space in comparison to steady-state techniques.
- Development of a general methodology for conducting efficient kinetic studies to maximise the benefit obtained from the automated reactor platform, by including aspects of traditional DoE. To conclude upon a kinetic model and its relative kinetic parameters, the experimental data undergo evaluation for model discrimination and precise parameter estimation.

1.2. Thesis outline

The thesis is structured into 7 chapters. The first chapter serves as the Introduction, outlining the general topic and establishing the aim and objectives of the thesis. Chapter 2 is dedicated to the literature review, which provides an overview of the advantages of miniaturised reactors and their characterisation in terms of mixing efficiency, both experimentally and computationally. It also delves into the integration of online and inline spectroscopy with small-scale reactors for the development of automated platforms for reaction kinetics. Additionally, hardware considerations and their interface with numerical methodologies for model identification and parameter estimation in automated systems are discussed.

Chapter 3 and 4 are dedicated to the modelling and employment of a SPSR in automated platforms for heterogeneously catalysed reactions. Chapter 3 presents the development of a CFD model to investigate the hydrodynamics and liquid-to-solid mass transfer in SPSRs. It compares the results of two different post-processing approaches for calculating the external mass transfer coefficient, leading to the extraction of a global correlation for external mass transfer evaluation.

Chapter 4 describes the employment of a SPSR in the context of obtaining the kinetics of a solid-liquid reaction as part of an automated platform, controlled by LabVIEW that incorporates online HPLC analysis. A methodology for the systematical screening of an extensive library of models for the continuous heterogeneously catalysed esterification reaction of levulinic acid with ethanol over Amberlyst-15 is developed and tested for parameter estimation and model discrimination.

In Chapter 5, the focus is shifted towards the fabrication of a m-CSTR that is integrated into the automated LabVIEW-controlled platform of Chapter 4 with minor modifications for real-time monitoring and estimation of the kinetic parameters of the synthesis of *n*-benzylidenebenzylamine in methanol with in-situ Raman spectroscopy. The reactor's mixing efficiency is evaluated in both micro- and macro-scale and its hydrodynamics are investigated through a CFD analysis.

Chapter 6 presents the utilisation of the m-CSTR, introduced in the previous chapter, for conducting intuitive ramp transient experiments for both single-variable and multi-variable ramps, aiming to merge the speed of transient experiments with the rapid detection and quantification offered by Raman spectroscopy. The results are compared against each other and juxtaposed with the steady-state experiments of Chapter 5, offering insights into precise kinetic parameter estimation and time efficiency of different experimental approaches.

Chapter 7 summarises the conclusions drawn from Chapters 3-6 and introduces potential extensions of the work, building upon the findings presented in this thesis.

Chapter 2. Literature review

The development of integrated continuous-flow platforms for chemical reaction kinetics represents a synergistic combination of different functional components, seamlessly interfacing hardware and software to facilitate efficient data flow [2]. The primary focus of this thesis lies in building automated platforms for acquiring kinetic data and developing kinetic models for heterogeneous catalytic and homogeneous non-catalytic reactions in liquid phase systems. This endeavour involves developing hardware with a central emphasis on reactor technology encompassing design, fabrication, and characterisation, coupled with inline analytical instruments for rapid data generation. The experimental platform components are integrated with software, leveraging the LabVIEW programming as a monitoring, and controlling human-machine interface, and algorithms tailored for modelling and parameter estimation. The subsequent section introduces these fundamental concepts in detail.

2.1. Building a kinetic model

Thermodynamics and kinetics are two fundamental aspects of chemical reactions, inextricably linked to one another. While thermodynamics discerns the viability of a reaction pathway, its directionality, and relevant constraints, thereby enabling the determination of the reaction's chemical equilibrium under specific conditions, it does not offer insights into the rate at which reactions proceed, the factors impacting these rates, or the intricate mechanisms at play. The exploration of these aspects falls within the purview of chemical kinetics [33]. The goal of kinetics can be summarised as determining the overall pathway, the reaction network and the reaction mechanisms and deriving quantitative equations that predict the reaction rate as a function of the local conditions, such as temperature, pressure, composition, phase state and the presence of catalysts [34]. The extraction of a reliable kinetic model is a necessary step for the design of reactors, facilitating their scale-up from laboratory sizes to commercialised plants, and the optimisation of process conditions to increase yield and selectivity [15]. Chemical kinetic models vary in complexity (i.e., first order or power law, Langmuir-Hinshelwood-Hougen-Watson (LHHW), n-lumped models, detailed mechanistic models, *ab initio*) and can be distinguished on three levels (i.e., intrinsic kinetic models, apparent kinetic models and models that include all transport effects in the kinetics) depending on how effectively kinetics have been separated from mass and heat transport effects [35]. The concept of a kinetic model in this thesis pertains to a mechanistic framework derived from a deep scientific comprehension of the chemical process, rather than mere statistical correlations between experimental variables and outcomes [36]. The process of constructing a kinetic model can be outlined in three key stages [37]:

1. Model formulation: This initial step involves distilling prior knowledge and available experimental evidence regarding the behaviour of the system into a suitable set of modelling

hypotheses. These hypotheses are then translated into mathematical expressions, representing the kinetic model equations.

2. Parameter estimation: Precise estimation of the kinetic parameters inherent in the model structure is essential and is achieved through the fitting of experimental data.

3. Model validation: Statistical techniques are employed to assess and validate the modelling hypotheses against experimental observations, ensuring the robustness and accuracy of the kinetic model.

A comprehensive overview of the modelling and parameter estimation, as it pertains to the statistical analyses conducted in this thesis, is provided in Chapter 4.

2.2. Miniaturised reactor technology for kinetic studies

2.2.1. Advantages and challenges of miniaturised reactors

Although, traditionally, kinetic measurements have been carried out in stirred, batch vessels, in the last two decades there has been a growing trend in acquiring kinetic data in continuous-flow systems (Figure 2-1) [1], a development partly attributed to the breakthrough of milli- and micro-scale technology [38].

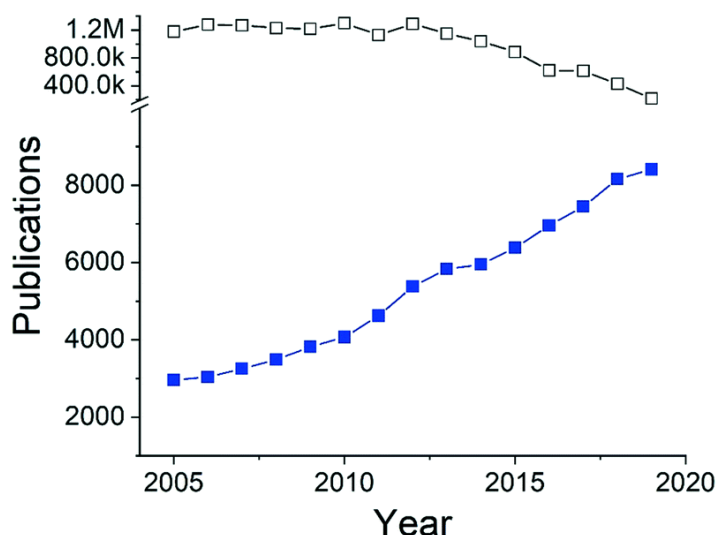


Figure 2-1. Trends of Google Scholar publications annually between 2004 and 2019, where: ■ = represents publications containing both “continuous flow” and “kinetics”, and □ = denotes publications featuring the word “chemistry” as a point of reference (adapted from [1] with permission from the publisher).

Continuous-flow micro and milli-reactors are characterised by their three-dimensional structures, with the inner dimensions ranging from 10-100 μm for microfluidic channels [39] to 1-10 mm for the millifluidic ones [40]. Hence, the defining feature of miniaturised reactors lies in their high surface-area-to-volume ratio, which surpasses that of conventional reactors by 10 to 50 times [41]. This attribute significantly enhances the rates of heat and mass transport, when compared to those observed in conventional sized reactors [42], or batch reactors [43]. The rapid heat transfer in small-scale systems promotes uniform temperature distribution, eliminating hot spots and enabling precise isothermal control, which proves particularly advantageous for the kinetic studies of strongly exothermic, endothermic and fast reactions [17-21]. Similarly, the heightened mass transfer rate, due to the much shorter diffusion pathways, can intensify mass transfer limited reactions [44] and minimise mass transfer resistances to facilitate the acquisition of intrinsic kinetics [45]. However, since every reaction system is unique, the assumptions of resistance-free operation regarding both mass and heat transfer need to be validated a priori. Only then can micro and milli-fluidic reactors be deemed suitable for intrinsic kinetic studies [46].

Furthermore, the small reaction volume in milli- and micro-scale reactor designs offers two distinct advantages. Firstly, it facilitates easy control of process parameters, promoting the exploration of wide operating process windows at elevated pressures and temperatures [3-5]. Secondly, the small reactor holdup reduces reagent consumption (although millifluidic systems typically require bigger reagent volumes than microfluidics), resulting in significantly less chemical waste and minimising exposure to hazardous or toxic compounds, compared to traditional testing methods [6, 7]. This proves convenient for kinetic studies involving reagents or catalysts that are challenging to obtain or prepare.

In contrast to kinetics acquisition in batch, where experimentalists must take samples from the reaction vessel at specific intervals, quench them appropriately, and analyse them offline, continuous-flow miniaturised reactors are readily coupled with inline and online analytical techniques for real-time reaction monitoring, either as standalone methods or in tandem, as it is explained in detail in Section 2.2. These tools continuously measure the reaction medium, significantly enhancing testing efficiency, reducing experimental errors in comparison to typical batch reactors [47], and increasing the amount of collected data. In the case of catalytic studies, *in situ* and *operando* spectroscopic techniques can provide crucial mechanistic information for the reaction mechanism, as well as on the catalytic activity and molecular structure [48-50].

The inherent advantages of the micro- and milli-scale reactors in terms of heat and mass transfer, as well as their easy integration with inline analytical techniques, have increased their efficiency in experimental kinetics investigations. This has led to significant advancements in the development of automated platforms that combine continuous-flow operation of miniaturised systems with sensing and feedback control [8] and yield substantial benefits, such as reducing the number of experiments required, conserving resources and freeing up researchers' time [51].

Among the pioneering automated microreactor systems is the one developed by Sugimoto et al. [52], which aimed at swiftly profiling the parameter space of a Sonogashira reaction and optimising reaction conditions, coupled with offline HPLC analysis (Figure 2-2a). Since then, automated flow reactors incorporating online/inline analysis have been successfully employed for unattended reaction monitoring [53, 54] (Figure 2-2b) and high throughput screening for discovery and optimisation purposes [55-57] (Figure 2-2c), some of which implement closed-loop control [58-63]. The complexity of these automated reactor platforms is steadily increasing, with examples now extending to gas-liquid-solid reactions [58, 64] (Figure 2-2d). Regarding the development of automated micro and milli-scale reactor platforms for identifying kinetic models, automated flow systems have been applied to investigate the

kinetics of relatively simple systems, such as liquid phase homogeneous [65-68] and gas-liquid reactions [29]. A current trend is the transition from automated to autonomous reaction kinetic platforms, achieved through the implementation of Model Based Design of Experiment (MBDoE) algorithms (as elaborated in Section 2.3.2) for homogeneous and heterogeneous catalytic liquid [51, 69] and gas phase [70, 71] systems (Figure 2-2e).

Despite the advantages of continuous miniaturised systems for kinetic data acquisition, there are still considerations of the benefits of performing a reaction in a flask. A major drawback of flow chemistry is the requirement for rapid reactivity [72]. Slow reactions with prolonged residence times can be difficult to handle, given that miniaturised systems typically operate under steady-state conditions that require 2-5 residence times before sampling [66]. This diminishes the inherent advantage of the micro- and milli- scale as it leads to the wastage of large amounts of reaction materials. Moreover, in scenarios involving solid-producing reactions or the use of catalysts in powder slurry form, the common occurrence of small channel clogging exacerbates these challenges. Another consideration pertains to the accessibility of equipment and the expertise barrier of the users. Although additive and nonadditive manufacturing techniques for miniaturised systems and the expanding market of readily available microfluidic components, such as fittings and connectors, facilitate relatively quick assembly and deployment of small-scale continuous flow reactors [73], transitioning from traditional batch reactors to flow systems often entails a significant capital investment [74].

The work presented in this thesis aims to tackle these challenges in acquiring kinetics in flow by integrating two complementary approaches: reactor design and technological advancement, particularly through the development of robust, automated platforms that incorporate efficient sampling methodologies. From a reactor design standpoint, miniaturised CSTRs [75, 76] have gained significant traction in fine chemical production for handling crystallisations [77] and, more recently, for the synthesis of functional nanomaterials [78]. Although the development of the m-CSTR technology holds promise for both research and production for increasing yield and overcoming mass-transfer limitations, there are no reports on their employment for acquiring reaction kinetics in continuous flow, to the best of the author's knowledge. Additionally, efficient sampling methodologies, such as implementing step changes and transient ramps of input variables, have been garnering increasing interest for obtaining reaction profiles [9, 10, 27, 66, 67, 79]. However, these studies remain limited due to the complexity of the experimental setups required and constraints posed by available analytical techniques.

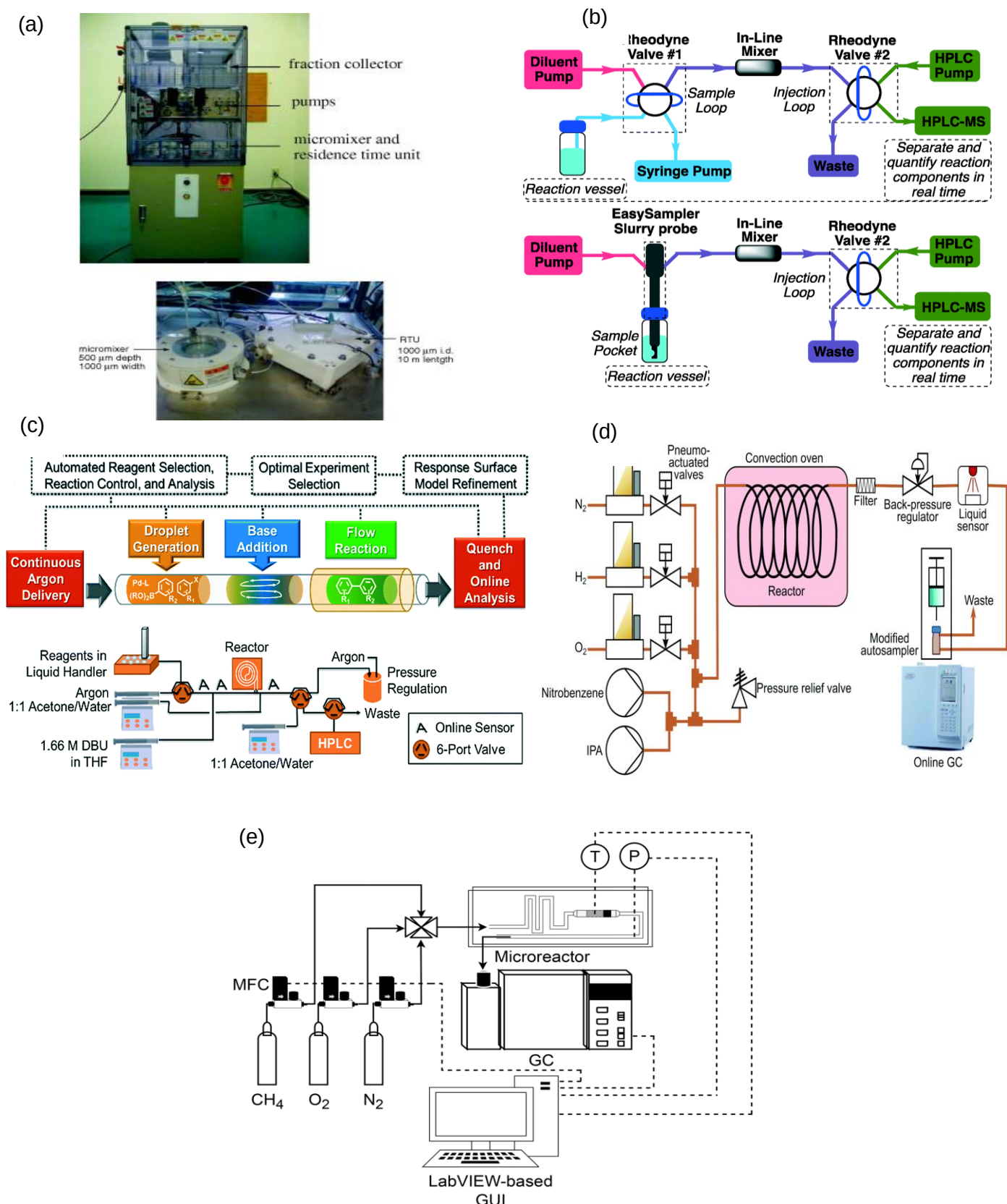


Figure 2-2. (a) Microreactor platform for optimisation of the Sonogashira coupling reaction (adapted from [52] with permission from the publisher), (b) Two possible configurations of an analytical platform coupled with Real-time HPLC-MS for homogeneous and heterogeneous reactions' monitoring (adapted from [54] with permission from the publisher), (c) Flow diagram for the automated Suzuki–Miyaura cross-coupling optimization (adapted from [57] under a Creative Commons Attribution 3.0 Unported

Licence), (d) Scheme of the reactor set-up used in a nitrobenzene hydrogenation coupled with online GC (adapted from [58] with permission from the publisher), (e) Autonomous experimental set up for methane oxidation reaction in a packed bed microreactor using online MBDoE methodology (adapted from [71] under a Creative Commons Attribution 3.0 Unported Licence.)

2.2.2. Characterisation of miniaturised reactors: Mixing efficiency and Residence Time Distribution

Reactor hydraulics play a pivotal role, delineating the pattern of fluid flow and the transport of species within the reactor. Optimal reactor design and selection for executing a desired reaction mandates a careful consideration and alignment of reactor characteristics with reaction kinetics. Mass and heat transfer properties emerge as paramount in determining reactor performance [80]. Therefore, in the realm of reaction kinetics in continuous flow systems, it is crucial to choose a suitable model to describe the reactor's behaviour. Hence, this section elaborates on mass transfer in the context of micromixing and Residence Time Distribution.

For better understanding of the mixing performance of a small-scale system, it is essential to elucidate the scales of the general mixing process. Mixing can be classified by three length scales: macromixing, mesomixing and micromixing [81, 82], as presented in Figure 2-3. Macromixing is defined as the mixing on the scale of the reactor, and it usually happens by bulk convection and turbulence. The mechanism for micromixing is mainly based on the smallest scale of motion (the Kolmogorov scale) dominated by molecular diffusion. Mesomixing is the intermediate scale between macro- and micromixing and it is intricately intertwined with the geometry of the system, e.g. to the position of the feed inlet in the case of stirred vessels [83]. It happens between the interface of two fluids and it is associated with engulfment and daughter vortices [84]. In most works, the term of mesomixing is not used and its effect is lumped into that of macromixing [85].

In micro-structured reactors that are generally characterised by laminar flow, mixing procedures are limited to diffusion and secondary flows [86]. Therefore, the typical sequence from macro- to micromixing is not observed [39]. However, this is not the case for turbulence-induced mixing procedures, such as miniaturised CSTRs with active agitation, where mixing phenomena in all three scales occur [87].

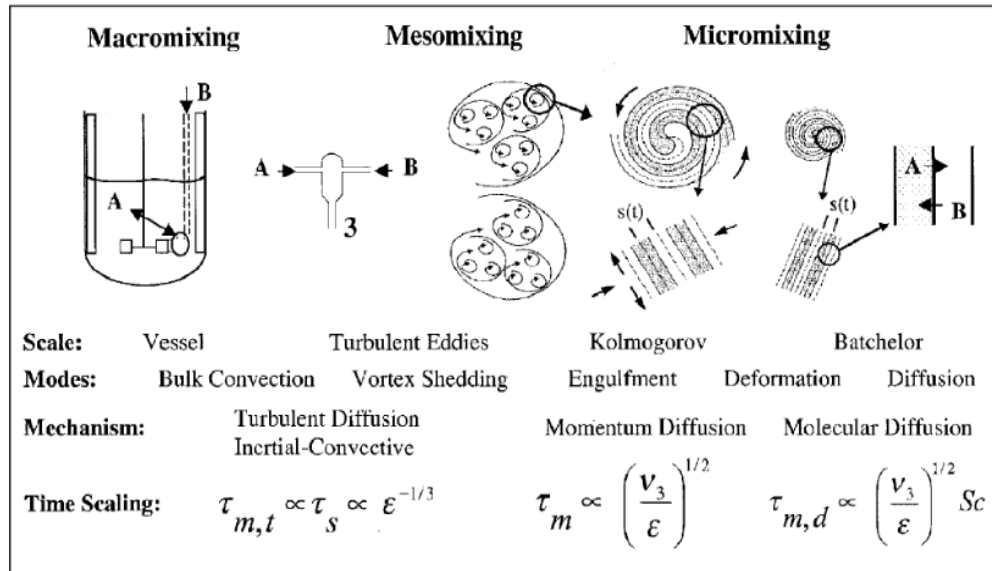


Figure 2-3. Scales of mixing and their relevant mechanisms (adapted from [82] with permission from the publisher).

2.2.2.1. Fundamentals of RTD modelling

In terms of macromixing, numerous experimental techniques, both intrusive and nonintrusive, exist to qualitatively and quantitatively assess its magnitude [88, 89]. In this thesis, the techniques employed to evaluate the reactor's performance rely on measuring the Residence Time Distribution (RTD) curves that serve as diagnostic tools of non-ideal flow patterns [90] for both large-scale and small-scale systems. Between 2019 and 2024, RTD was featured in over 3,000 articles indexed by the Web of Science Core Collection (WoS) [91], with major keyword clusters identified, as illustrated in Figure 2-4.

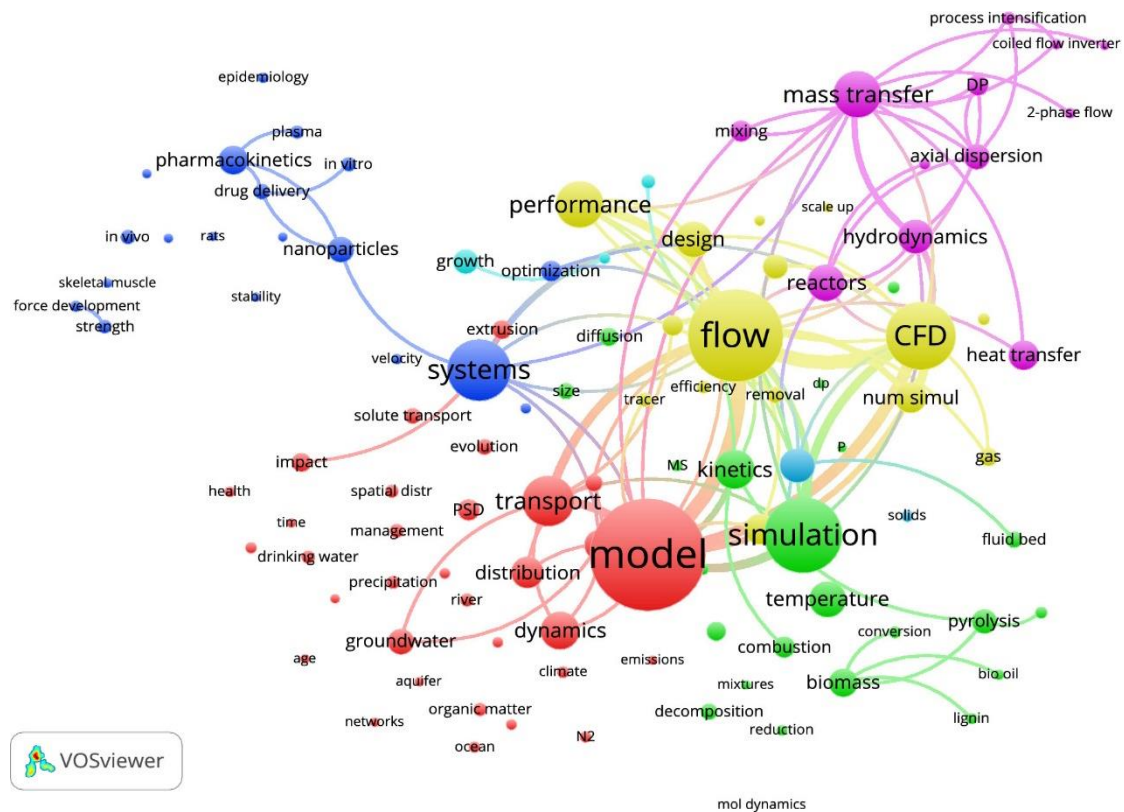


Figure 2-4. RTD bibliometric map, showcasing the 100 most common keywords found in the top 10,000 cited articles (adapted from [92] with permission from the publisher).

The RTD profiles are created by monitoring a tracer, ideally an easily detectable, inert, non-volatile, non-absorbed solute, able to follow the fluid path along the reactor, without disrupting the flow [93]. The two most used methods of injection of a tracer in a system are as a pulse or a step input [90]. Various tracer detection methods are employed in laboratory and industrial-scale tests. For liquid applications, common techniques include the use of colourful dyes, the concentration of which is detected and measured by UV-vis spectrophotometers [94-96] and conductivity measurements of NaCl and KCl solutions [97-99]. Gas concentration is often tracked using online mass spectrometry [100] and thermal conductivity detection [101]. Near Infrared (NIR) spectroscopy has been utilised for solid phase systems [102], while radioactive tracers have, also, been widely employed for the RTD studies in a variety of reactors [103].

When a tracer is introduced into a system, either as a pulse injection (approximated as Dirac delta pulse) or as a step injection, the change in the concentration, denoted as c , over time, t , is essentially measured at the outlet, resulting in the generation of the tracer concentration profile, referred to as the C-curve. The most used curve that serves as a metric to characterise the behaviour of fluid dynamics in a reactor is the RTD function, designated as $E(t)$ (E-curve). The $E(t)$ is correlated to the C-curve by normalisation, as shown in Equation 2-1. The RTD function $E(t)$ represents the temporal duration various fluid elements spend in the reactor and its peak indicates the time where most of the tracer material reaches the outlet [90].

$$E(t) = \frac{c(t)}{\int_0^{\infty} c(t)dt} \quad (2-1)$$

The integral of the E-curve gives the cumulative distribution function, $F(t)$ that represents the fraction of the tracer that has been in the vessel at time t or less [90].

$$\int_0^t E(t)dt = F(t) \quad (2-2)$$

The theoretical space time of the fluid flowing through the reactor volume V with a volumetric flowrate Q_0 is calculated as shown in Equation 2-3.

$$\tau = \frac{V}{Q_0} \quad (2-3)$$

Since $E(t)$ is a normalised distribution with integral equal to 1, it is possible to calculate statistical indicators directly from the E-curve. To evaluate the reactor's performance, apart from visually comparing the shape of the RTD curve for diagnostic purposes (double peaks, unsymmetrical distributions, or long tails) to the ideal RTD [104], two parameters are commonly used in practice, the mean residence time $\bar{t}$, as well as the variance, σ^2 . The mean residence time (known as first moment), $\bar{t}$, of a real reactor is calculated based on Equation 2-4 and compared with the theoretical space time, τ (Equation 2-3).

$$\bar{t} = \int_0^{\infty} tE(t)dt \quad (2-4)$$

The second moment, variance (σ^2), represents the spread of the curve (Equation 2-5). The larger the variance the higher the amplitude of the distribution and, thereby, an elevated deviation from plug flow [92].

$$\sigma^2 = \int_0^{\infty} (t - \bar{t})^2 E(t)dt \quad (2-5)$$

Another way to represent the RTD function is in its normalised form $E(\theta)$, defined based on the dimensionless mean residence time, θ , mathematically described by Equations 2-6 and 2-7, respectively.

$$E(\theta) = \bar{t}E(t) \quad (2-6)$$

$$\theta = \frac{t}{\bar{t}} \quad (2-7)$$

To quantify deviation from ideal perfectly mixed or plug-flow behaviour, caused by channelling of fluid, recycling of fluid and by the existence of stagnant regions, models can be used to represent flow in real vessels, for scale-up and diagnosis. The axial dispersion model (ADM) and tanks-in-series model (TISM) are one-parameter models that describe partially mixed reactors with a finite level of mixing, which cannot be described by either a CSTR (assuming perfect mixing) or a PFR (assuming no mixing) models [105].

2.2.2.1.1. Axial Dispersion Model

The axial dispersion model (ADM) can be used to describe real flow that deviates from ideality, due to molecular and eddy diffusion and non-uniform distribution [106]. The model considers the flow inside the vessel to be plug flow and superimposes a certain degree of back-mixing, quantified by the presence of the axial dispersion coefficient term, D_{ax} , independently of the position in the vessel [104], as shown in Equation 2-8. The model assumes that the radial velocity and concentration variations are negligible.

$$\frac{\partial c}{\partial t} + u \frac{\partial c}{\partial x} = D_{ax} \frac{\partial^2 c}{\partial x^2} \quad (2-8)$$

Where, u is the tracer convective velocity in the x -direction (m/s). In dimensionless form, Equation 2-8 transforms into Equation 2-9.

$$\frac{\partial c}{\partial \theta} = \frac{1}{Pe} \frac{\partial^2 c}{\partial z^2} - \frac{\partial c}{\partial z} \quad (2-9)$$

$$z = \frac{ut + x}{L} \quad (2-10)$$

Where, L is the characteristic system length (m) and Pe is the Peclet number, defined by Equation 2-11, as the ratio between convection and axial dispersion.

$$Pe = \frac{uL}{D_{ax}} \quad (2-11)$$

Practically, Pe is the single parameter in the dispersion model, which as it increases from 0 to infinity, ∞ , the flow pattern in the reactor changes from mixed flow (large dispersion) to plug flow (negligible dispersion). Experimental data can be fitted in the ADM for small degrees of dispersion ($Pe < 100$), the analytical solution for the E-curve and the variance, σ^2 is reported in Equations 2-12 and 2-13. For the case of large deviation from plug flow ($Pe > 100$), where the entrance and exit effects become important, the analytical expression of the E-curve is only available for open-open boundary condition (Equation 2-14, 2-15). For the expression of other designated boundary conditions (close-close, open-close) as well as further details on the ADM can be found in Reaction Engineering textbooks [90, 104].

$$E(t) = \sqrt{\frac{u^3}{4\pi DL}} \exp \left[-\frac{(L - ut)^2}{4DL/u} \right] \quad (2-12)$$

$$\sigma^2 = 2 \left(\frac{DL}{u^3} \right) \quad (2-13)$$

$$E(t) = \frac{u}{\sqrt{4\pi Dt}} \exp \left[-\frac{(L - ut)^2}{4Dt} \right] \quad (2-14)$$

$$\sigma^2 = 2 \left(\frac{D}{uL} \right) - 2 \left(\frac{D}{uL} \right)^2 \left[1 - e^{-\frac{uL}{D}} \right] \quad (2-15)$$

2.2.2.1.2. Tanks-in-series Model

Yielding roughly equivalent results, for reactors with limited back-mixing, the tanks-in-series model (TISM) can be used to describe deviation from ideal flow, instead of the ADM [107]. The non-ideal reactor consists of a cascade of N_{tanks} -equally sized ideal CSTRs that are connected in series, such that the outlet of one CSTR feeds the inlet of the next. The RTD curve and the relevant metrics are given by Equations 2-16 to 2-18.

$$E(t) = \left(\frac{N_{\text{tanks}}}{\bar{t}} \right)^n \frac{t^{N_{\text{tanks}}-1}}{(N_{\text{tanks}} - 1)!} e^{-tN_{\text{tanks}}/\bar{t}} \quad (2-16)$$

$$\bar{t} = N_{\text{tanks}} \bar{t}_i \quad (2-17)$$

$$\sigma^2 = \frac{\bar{t}^2}{N_{\text{tanks}}} \quad (2-18)$$

As N_{tanks} , the single parameter in the TISM, increases from 1 to ∞ , the flow pattern in the reactor changes from complete mixing (CSTR) to no mixing (PFR). In comparison to ADM, TISM is simpler as it requires the solution of algebraic equations instead of a differential one and can be used with any kinetic model [90]. To overcome the limitation of integer N_{tanks} values, imposed by the factorial expression $(N_{\text{tanks}} - 1)!$ in Equation 2-15, a gamma function model (Equation 2-19), able to describe bypassing ($N_{\text{tanks}} < 1$) can replace the denominator of Equation 2-16 [108] with the satisfaction of the relevant conditions (Equations 2-20 to 2-22).

$$\Gamma(N_{\text{tanks}}) = \int_0^\infty x^{N_{\text{tanks}}-1} e^{-x} dx \quad (2-19)$$

$$\Gamma(0) = \Gamma(1) = 1 \quad (2-20)$$

$$N_{\text{tanks}} \Gamma(N_{\text{tanks}}) = \Gamma(N_{\text{tanks}} + 1) \quad \forall N_{\text{tanks}} \in \mathbb{R} \quad (2-21)$$

$$\Gamma(N_{\text{tanks}}) = (N_{\text{tanks}} - 1)! \quad \forall N_{\text{tanks}} \in \mathbb{N} \quad (2-22)$$

It shall be noted that the reactor Peclet number for mass dispersion is often interchangeably referred to as the Bodenstein number, Bo , in reacting systems [90]. To link the two models,

for small deviation from plug flow, the number of n CSTRs is correlated to the Peclet number Pe by Equation 2-23 [109].

$$N_{\text{tanks}} = \frac{Pe}{2} + 1 \quad (2-23)$$

2.2.2.2. Micromixing

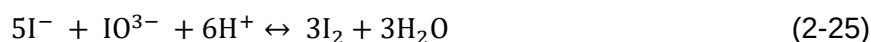
Since chemical reactions are molecular-level processes, mixing at the molecular scale (micromixing) directly influences their progression, impacting conversion and selectivity [110], particularly in rapid reactions, such as those found in organic synthesis, precipitation, polymerisation and crystallisation [111]. Therefore, investigating micromixing phenomena in chemical reactors requires fast test reaction systems, meeting specific criteria: a characteristic reaction time that is either shorter than or comparable to the micromixing time, well-defined reaction mechanisms and kinetic equations, easily achievable quantification of reaction products (e.g. based on inline spectroscopic techniques, such as UV-Vis) and a safe and cost-effective operation [85]. The mostly used test systems are categorised into consecutive competitive reactions and parallel competitive reactions [112], as shown in Table 2-1.

Table 2-1. Consecutive and parallel competitive reaction schemes.

Consecutive competitive reaction		Parallel competitive reaction	
$A+B \rightarrow R$	(R1)	$A+B \rightarrow R$	(R1)
$R+B \rightarrow S$	(R2)	$C+B \rightarrow S$	(R2)

The groundwork of characterising micromixing using competitive reaction systems has been established by Bourne and Villiermaux. Common reaction systems include the diazo coupling [113], Bourne III [114], Bourne IV [115, 116], and Villiermaux–Dushman reaction systems [117-119]. Among these, the iodide-iodate test (Villiermaux-Dushman reaction) and the diazo coupling test (between naphthols and diazotized sulphanilic acid) are widely employed methods, the former based on the competitive parallel reaction system and the latter combining a system of two competitive parallel reactions and two competitive consecutive reactions. In this thesis, the iodide-iodate test reaction is chosen for micromixing quantification, and its methodology is presented in detail.

Although initially designed for stirred tank reactors, the Villiermaux-Dushman reaction system has been adapted for use as a standard test reaction in micromixing devices [112]. The reaction scheme for the Villiermaux–Dushman protocol can be described as follows [119]:



The acid-base neutralization reaction (Equation 2-24) and the redox reaction (Equation 2-25) are competitive reactions for the available protons supplied by the sulfuric acid, with the former being quasi-instantaneous and the latter, between iodate and iodide that produces iodine, being rapid, but with a significantly lower reaction rate than that of the neutralization reaction. When micromixing is not instantaneous, the redox reaction proceeds due to incomplete consumption of protons, resulting in the generation of iodine. The generated iodine from the redox reaction reacts further with excess iodide to reversibly generate triiodide ions, as shown in Equation 2-26.



The triiodide formed has a distinct yellow colour and a strong UV-Vis absorption peak at the wavelength of 353 nm and can be quantified using the Lambert-Beer law [120], as presented in Equation 2-27.

$$[I_3^-] = \frac{OD}{\epsilon_{353} l_{\text{optical}}} \quad (2-27)$$

Where, OD denotes the optical density (or absorbance), ϵ_{353} the extinction coefficient of triiodide at 353 nm ($L \cdot mol^{-1} \cdot cm^{-1}$) and l_{optical} the optical path length within the measurement cell (cm).

To apply this methodology in a miniaturised system and determine its mixing time, it is imperative to define the kinetics of the reactions. The acid-base neutralisation reaction is assumed to be instantaneous ($k = 10^{11} L/mol \cdot s$) [121]; hence, the kinetic rate expression of the redox reaction (Equation 2-28) is the one that has been experimentally determined [121, 122] and an empirical model can be used [122].

$$r = k[H^+]^2[I^-]^2[IO_3^-] \quad (2-28)$$

With k [$mol^4/L^4/s$] denoting the kinetics constant that depends on the ionic strength of the mixture, μ as

$$\log_{10}(k) = 9.28105 - 3.664\sqrt{\mu} \text{ for } \mu \leq 0.166M \quad (2-29)$$

$$\log_{10}(k) = 8.383 - 1.5115\sqrt{\mu} + 0.237\mu \text{ for } \mu \geq 0.166M \quad (2-30)$$

Where μ is defined as

$$\mu = \frac{1}{2} \sum_{i=\text{all species}} c_i z_i^2 \quad (2-31)$$

In which, c_i is the concentration of the ion of reacting species i (mol/m^3) and z_i is its charge number.

The equilibrium constant of the triiodide formation K_B (Equation 2-32) is related to the operating temperature T (K) by Equation 2-33 [123].

$$K_B = \frac{[I_3^-]}{[I^-][I_2]} \quad (2-32)$$

$$\log_{10}(K_B) = \frac{555}{T} + 7.355 - 2.575\log_{10}(T) \quad (2-33)$$

The degree of mixing efficiency can be quantitatively described by the segregation index X_s , and the order of mixing time, t_m , both parameters' estimation relying on the selection of a mixing model, able to describe the mechanistic properties of the integration of the two fluid streams. Common mixing models are the Interaction by Exchange with the Mean (IEM), incorporation, and engulfment models [124] [125]. Although IEM appears to be less accurate among the deterministic micromixing models [126], the models exhibit relatively low variation of calculated mixing times [127], the simple IEM model [128, 129] was chosen in this thesis to provide a baseline quantifiable for comparison of mixing times. The IEM model assumes that the two streams exchange mass with a characteristic time constant equal to the mixing time and involves solving various differential mass balance equations for the mass exchange between the two mixing streams in Villermoux-Dushman test reaction to obtain the concentration of triiodide (and subsequently determine the segregation index, X_s) and can be expressed as follows [125].

$$\frac{dc_{i,1}(t)}{dt} = \frac{\langle c_i(t) \rangle - c_{i,1}(t)}{t_m} + R_{i,1} \quad (2-34)$$

$$\frac{dc_{i,2}(t)}{dt} = \frac{\langle c_i(t) \rangle - c_{i,2}(t)}{t_m} + R_{i,2} \quad (2-35)$$

$$\langle c_i(t) \rangle = \alpha_{\text{acid}} c_{i,1}(t) + (1 - \alpha_{\text{acid}}) c_{i,2}(t) \quad (2-36)$$

Where c_i is concentration of species i (mol/m^3), $\langle c_i \rangle$ is the average concentration of species i across both the acid (denoted by subindex 1) and the buffer (denoted by subindex 2) solutions (mol/m^3), R_i ($\text{mol/m}^3 \cdot \text{s}$) represents the reaction rate of species i (obtained from Fournier et al. [117]), t_m is the mixing time (s) and α_{acid} is the fraction of the acid solution volume added.

The segregation index X_s is defined as

$$X_s = \frac{Y}{Y_{ST}} \quad (2-37)$$

$$Y = \frac{2V_2([I_2] + [I_3^-])}{V_1[H^+]_0} \quad (2-38)$$

$$Y_{ST} = \frac{6([IO_3^-]_0)}{6[IO_3^-]_0 + [H_2BO_3^-]_0} \quad (2-39)$$

Where, Y is the ratio of acid mole number consumed by the redox reaction (Equation 2-25) divided by the total acid mole number injected and Y_{ST} is the value of Y when the mixing process is infinitely slow, i.e. the neutralization reaction (Equation 2-24) and the redox reaction become quasi-instantaneous compared to the mixing time, t_m .

Detailed insights regarding the derivation of the segregation index X_s and the system of mass balance equations to be solved by the IEM mixing model can be obtained from the works of Guichardon, Falk, and Commenge [112, 119]. Equations 2-37 to 2-39 are used to determine the segregation index X_s based on the initial iodide concentration and the triiodide concentration post-mixing. The correlation between the mixing time and the triiodide concentration or the segregation index, X_s can be established by specifying the initial reagent concentrations and solving the IEM model [117] for various mixing times. Figure 2-5 presents the relationship between the micro mixing time and the segregation index, for an optical length of 1 cm [130].

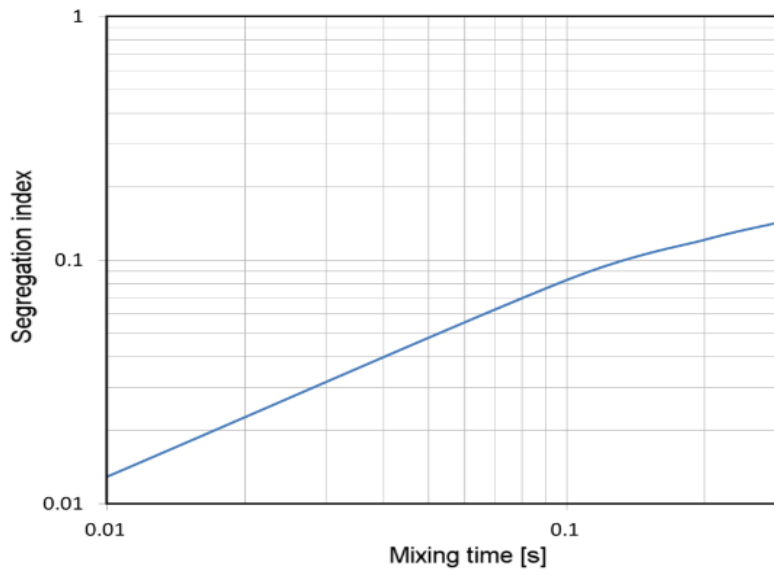


Figure 2-5. Segregation index vs. mixing time estimated using the IEM model for the Villiermaux-Dushman reaction scheme. Concentrations of buffer solution were KI: 0.0117 M, KIO_3 : 0.0023 M, NaOH: 0.0909 M, H_3BO_3 : 0.1818 M. Concentration of H_2SO_4 was: 0.07 M (adapted from [130] with permission from the publisher).

2.2.2.3. Computational Fluid Dynamics for mixing characterisation

With the progressive enhancement of high-performance computing capabilities, numerical simulation based on computational fluid dynamics (CFD), has emerged as a dependable approach for analysing intricate flow patterns, mixing characteristics, and transport

mechanisms [131]. While experimental validation remains necessary, the CFD methodology can synergistically guide and accelerate experimental progress [132], due to its capacity to furnish local flow data in 2-D or 3-D spatial dimensions, which might be challenging to obtain otherwise. Furthermore, its cost-effectiveness, efficiency, and adaptability are noteworthy, as it allows for the adjustment of design and operational parameters during the simulation process, holding potential to improve and optimise the design of miniaturized systems, or even inform pre-fabrication considerations [133].

In continuous flow systems, assessing the non-ideality of macromixing by analysing the shape of the RTD curve lacks spatial information crucial for defining the state of mixing within the reactor [134]. Consequently, CFD is employed to predict local velocity and concentration variations, the spatial integration of which determine the RTD shape at the reactor's outlet [135]. Numerical RTD primarily focuses on two approaches. The first approach mirrors experimental procedures, where the tracer is introduced either as a pulse or a step change. Initially, the flow equations (Navier-Stokes equations for momentum and a turbulence model if applicable) are solved using a steady-state approach. The tracer fluid concentration, considered as a species with properties akin to the solvent to minimise its impact on the flow field, is defined at the outlet by solving the convective-diffusion equation in transient mode [136]. Alternatively, the Lagrangian Particle tracking method can be employed that involves injecting a large number of passive tracer particles into the flow, then solving ordinary differential equations using Newton's law of motion to track their trajectories, with the residence time for each particle determined by integrating over particle velocity and travel distance [137-139]. Both methodologies require the use of time-dependent solvers, where applying a small time-step size is critical to the accuracy of the solution and therefore, it can be proven computationally expensive for capturing the tail of the distribution [140].

Recent work by Liu [141-143] and Liu and Tilton [140] has prompted a re-evaluation of the conventional RTD approach to characterise mixing in reactor systems. Their work reintroduces the concept of spatial distribution of mean age as a measure of mixing [144, 145]. Mean age, governed by a transport equation analogous to the Navier-Stokes equation, offers computational advantages by leveraging steady-state solvers commonly employed in CFD simulations. This shift significantly reduces the computational effort required for macromixing analysis. Furthermore, spatial mean age offers distinct advantages over the RTD function by providing clear insights into the size and location of the dead zones and short-circuiting paths. While it does not directly yield the $E(t)$ function of the RTD, the mass-flow weighted average of the mean age at the exit corresponds to the mean residence time, and other parameters, such as the variance and coefficient of variance, derived from the spatial mean age distribution mirrors that of the RTD, ensuring consistency in assessing mixing efficiency [140]. This

method extends the capabilities of current CFD for quantitative characterization of both spatial and temporal nonuniform mixing in reactors.

In the case of modelling micromixing, in addition to solving the flow field, the introduction of the chemical reaction in the species transport equations must be considered, which significantly complicates simulations. Modelling mixing at a molecular level not only requires knowledge of the kinetic rate of the test reactions, such as the iodide–iodate reaction, but also depends on the concentration field and rate of species production. Consequently, to evaluate micromixing, the component concentrations at the simulating-cell scale, a scale much smaller than the minimum size of the grid, must be obtained first and then applied to the reaction kinetics [146]. To address these challenges, models that describe the relationship between fluid mixing and chemical reactions have been developed [147-149]. One of the most accurate and widely used models is the Finite-Rate/Eddy Dissipation Model (FR/EDM) [146, 150-152]. In the FR/EDM, the reaction rate is governed by both kinetics and mixing comprising two parts: the finite-rate model (FRM) that solves the chemical reactions by using Arrhenius equation-calculated intrinsic reaction rates and the energy dissipation model (EM) describes a reaction where turbulent mixing controls its rate. The final reaction rate equals the smaller of the two [151].

2.3. Integration of online analysis in miniaturised technology

While the potential of miniaturised reactors for kinetic model development has been extensively demonstrated for single- [153-155] and multi-phase [46, 156, 157] systems, the need persists for the seamless integration of analytical tools to enable online and inline process monitoring [158]. In the ideal scenario, inline characterisation should be fast (quasi real-time), sensitive enough to detect trace-amounts of intermediates that may escape offline analysis and non-invasive to prevent any modification or destruction of the analysed sample [159].

The coupling of micro- and milli-fluidic platforms with in-situ and operando chromatographic and spectroscopic techniques revolutionises real-time acquisition of reaction information and expedites the retrieval of kinetic data. This integration serves not only as a diagnostic tool for monitoring the operational status of the reactor but also aids in identifying potential causes of malfunction [160]. Consequently, optimising reaction conditions and conducting kinetic studies become more reliable compared to the traditional 'black-box' approach, which relies on offline product analysis. Each analytical tool brings its own set of strengths and weaknesses, facilitating both qualitative and quantitative analyses. High Performance Liquid Chromatography (HPLC), Ultrahigh Performance Liquid Chromatography (UHPLC) and Gas Chromatography (GC) are ubiquitous in chemical synthesis laboratories and have been used extensively in automated platforms [51, 61, 70]. A pump is utilised to transport the sample into a loop on a high-pressure injection valve integrated into the flow path ahead of a column. Method development and testing under various reaction conditions (pressurized vs. unpressurized, homogeneous vs. heterogeneous, heated vs. room temperature) are necessary to validate the sampling system before drawing any inferences from collected reaction data [161]. This thesis section focuses on the fundamental physical principles and existing frameworks specifically tailored for the integration of commonly used spectroscopic detection methods (Fluorescence, UV-Vis, Infrared, Raman and NMR spectroscopy) with miniaturised systems, some examples of which can be found in Figure 2-6.

2.3.1. Fluorescence spectroscopy

Fluorescence spectroscopy is grounded in the detection of light emission from excited singlet states of fluorescent substances (fluorophores) to permissible vibrational levels in the electronic ground state [162]. The resulting emission spectra, recorded at a single constant excitation wavelength, provide insights into the chemical structure of the fluorophore, including the structure of the different vibrational levels. Additionally, fluorescence intensity infers the concentration of the fluorophore [163]. The heightened sensitivity of fluorescence spectroscopy, in the nanomolar or picomolar range, renders it particularly advantageous in applications where sample volumes are limited [164, 165]. The application of fluorescence detection has become pervasive in the assessment of mixing characteristics within micro-channels. Laser-induced fluorescence (LIF) stands out as a primary method, where the concentration of fluorescent tracers correlates monotonically with the excited fluorescence intensity [166-168]. Additionally, reaction-sensitive fluorescents have been employed, exhibiting changes in measured fluorescence intensity corresponding to the progression of chemical reactions [169, 170]. Beyond its role in evaluating mixing properties, fluorescence spectroscopy has found extensive use in various kinetic studies [171, 172] with its main application found in the estimation of kinetic parameters associated with enzymatic reactions [173-175].

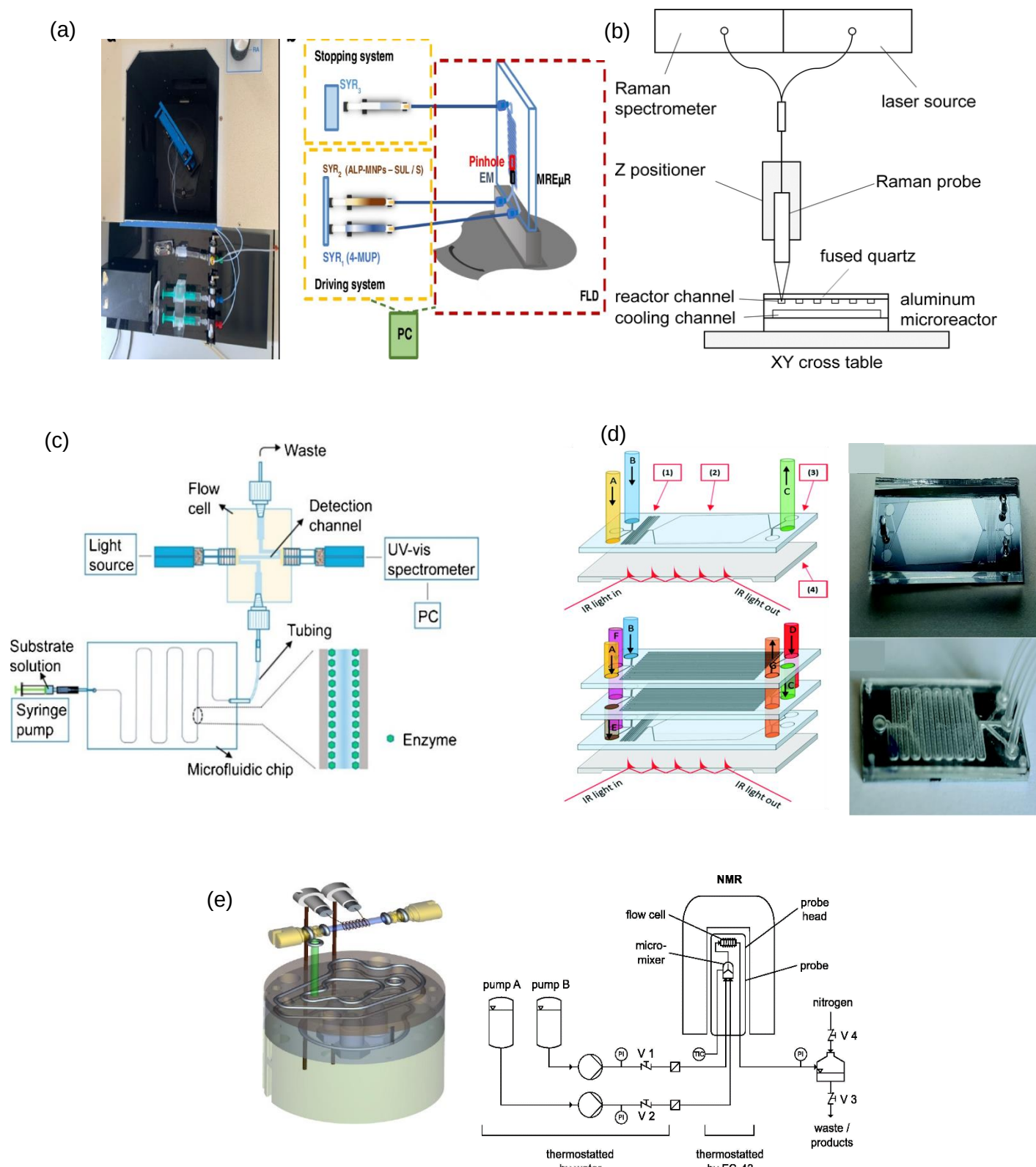


Figure 2-6. (a) A microfluidic stopped-flow system (μ SFS) with an integrated spectrofluorometer for rapid kinetic reactions in bioanalysis (adapted from [175] under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International Licence), (b) Schematic of the experimental setup for the inline Raman spectroscopic measurements of the synthesis of 3-piperidino propionic acid ethyl ester in a microreactor (adapted with permission from [176]. Copyright 2015 American Chemical Society), (c)

Illustration of a microfluidic chip with immobilised enzymes, integrated with a UV/vis spectrophotometric detection, for food ingredient analysis (adapted from [177] with permission from the publisher), (d) Microfluidic chips on Si-ATR for kinetics of a Paal–Knorr reaction (adapted from [178] under the Creative Commons Attribution-NonCommercial 3.0 Unported Licence) and (e) Online NMR set-up using a micro-reactor probe head as reactor and detector for quantitative analysis of fast esterification reactions (adapted from [179] with permission from the publisher).

2.3.2. UV–vis spectroscopy

Typically employed in conjunction with chromatography, UV-vis spectroscopy is based on the measurement of light absorption in the specific range of 200–700 nm by specific functional groups within the sample molecule, induced by electronic transitions when electrons interact with photons that correspond to this wavelength [180]. Parameters, such as the position of the maximum absorption bands and the intensity of these bands, characterise the UV-Vis spectrum, varying based on the molecular structure of the compounds under examination [181]. For quantitative analysis, the Beer-Lambert law is applied [180]. Achieving micromolar detection limits under specific optical configurations [182], UV-vis spectroscopy integrates seamlessly into miniaturized systems through various methods. Inline flow-through transmission cells connected to the reactor's outlet [183, 184], optical cuvettes and probes [185], out-of-plane integration involving a UV-Vis microscope or a UV-vis reactor sandwiched between perpendicular optical fibres [186-188] and in-plane integration that incorporates etched detection cells [189] or waveguides [190] on miniaturised chips provide versatility in monitoring and quantifying reaction species especially in liquid media [187, 191, 192].

2.3.3. Infrared spectroscopy

In contrast to UV-vis spectroscopy, which rely on larger energy absorbances associated with electronic transitions, Infrared (IR) spectroscopy focuses on the much smaller energy absorbances that occur between various vibrational and rotational states within a molecule. The absorption of IR radiation is limited to molecules undergoing a net change in dipole moment during vibrational and rotational motions, making it a powerful tool for analysing molecular structures [193]. Infrared spectroscopy is divided into three regions according to the working wavelength range (Table 2-2). In the context of this thesis, when referring to IR spectroscopy, it specifically pertains to the Fourier-transformed infrared (FTIR) technique [194], operating in the mid-infrared region.

When coupling with milli and micro-systems, the spectra of the reaction mixture can be effectively measured in either transmission [195] or reflection mode [196] on either an FTIR microscope stage or a sample compartment connected to an FTIR spectrometer.

Table 2-2. Overview of IR ranges and bands.

Type of IR spectroscopy	Range	Bands observed/Use
Near-infrared (NIR)	0.8 to 2.5 μm	Bands from electronic transitions, overtones and combinations modes [197, 198]. Commonly used for organic compounds containing a hydrogen atom, e.g. O-H, N-H and C-H bonds.
Mid-infrared (MIR)	2.5 to 25 μm	Fundamental bands of molecular vibrations in nearly all organic compounds [199-202]. Divided into the “functional group” (frequencies between 4000 and 1500 cm^{-1}) and “fingerprint” region (below 1500 cm^{-1}), the latter involving molecular vibrations unique to each compound [193].
Far-infrared (FIR)	25 μm to 1 mm	Bands associated with intermolecular, lattice and skeleton vibrations [203, 204]. Primarily used for analysing stretching vibrations in molecules with heavy atoms, including inorganic and metalorganic compounds [205].

While absorbance can be easily correlated with the local concentration of chemical species through the Beer-Lambert law, analysing a stream inside a miniaturised reactor in transmission mode presents challenges. One of the main difficulties emerges from the necessity for a fully mid-IR transparent fabrication material [206]. Although silicon [195, 207] and CaF_2 [208] are prevalent choices for wafer etching, silicon’s opacity in the visible region and CaF_2 ’s cost and brittleness [209] are restrictive factors. Additionally, the shallow depth of the reactor channels needed to ensure a good signal-to-noise ratio (SNR) in the acquired spectra regardless of the solvent absorption [195, 209], imposes restrictions on the flow range, due to pressure drop. For this reason, IR transmission flow-through cells that can be coupled with the outlet of the reactor [210], have been developed for monitoring reaction processes.

The internal specular reflectance technique, known as Attenuated Total Reflectance (ATR), is an approach very well adapted to small-scale experimentation. It relies on the total internal reflection that can occur at the interface between an element with a high refractive index (ATR crystal) and the medium to be analysed. The evanescent wave, generated by total internal reflectance, protrudes only a few microns (0.5 μm - 5 μm) beyond the crystal surface and into the sample [211] and, as it is on the order of the wavelength of the incident light, it greatly mitigates solvent interference [212, 213]. This is advantageous for studying aqueous samples, where the absorption of water is high. Moreover, the technique can provide online monitoring of reactions by analysis of reactant/products in either the bulk fluid phase or at the catalyst surface [214]. ATR-FTIR spectroscopy can be integrated with miniaturised reactors, either as a flow-through cell [67], such as the ReactIR flowcell [215-217], or by using the surface of the crystal itself to form on side of the microfluidic device [178, 210, 218].

2.3.4. Raman spectroscopy

In tandem with IR spectroscopy and often complementary to it, Raman spectroscopy is a non-destructive method that serves as a valuable tool for real-time and in-situ monitoring of chemical reactions. Raman spectroscopy relies on measuring the inelastic scattering of monochromatic light, typically from a laser source with radiation in the ultraviolet, visible or near-infrared range, interacting with a sample molecule [219, 220]. When subjected to monochromatic light irradiation, a significant portion of the beam scatters without altering the frequency of the photons, resulting in the maintenance of the same energy before and after irradiation (a phenomenon known as elastic scattering). However, a small fraction of the scattered photons undergoes inelastic scattering (also known as Raman scattering), during which, the energy of the incident photon creates an energy gap between two electronic energy levels in the molecule [220, 221], leading to a shift in the emitted photon's frequency (Raman shift) [222]. This interaction results in a scattered light spectrum with distinct frequency differences, providing information about the fundamental vibrations within the molecule and creating a unique molecular fingerprint [220]. Raman spectroscopy is versatile, extending its utility beyond the analysis of organic compounds to include inorganic compounds, with the capability to reveal bands well below 400 cm^{-1} [205]. Its distinctive advantage becomes evident in applications involving aqueous solutions, where water's weak scattering does not interfere significantly with spectral data [222] and with IR-inactive species, exemplified by symmetric vibrations of nonpolar groups, where Raman spectroscopy outperforms IR [205].

In the realm of miniaturised reactors, Raman spectroscopy exhibits notable compatibility with direct on-chip detection of reagents expediting the optimisation of the reaction process. Leveraging visible light lasers, Raman spectroscopy facilitates convenient use with optically transparent materials, particularly glass; an added benefit that stands in contrast to UV and IR measurements [223]. Raman spectroscopy is mainly integrated with miniaturised systems for reaction monitoring via the employment of Raman microscope spectrometers [223-227], usually equipped with confocal optics for discrimination between points of different depths within the sample, Raman cells with integrated probes [183] and open beam focus probes [9, 68, 228] both for single-phase or multiphase flow conditions. Wave confined Raman spectroscopy (WCRS) has also been reported, an alignment-free approach that uses a pair of embedded waveguides in a microfluidic channel to excite and collect the Raman signal [229].

For the detection of chemicals at very low concentrations in the liquid phase (e.g., in the nanomolar or picomolar range), signals obtained using conventional Raman spectroscopy are considerably weak. Despite the inherent challenge of weak signals in conventional Raman

spectroscopy, innovative techniques such as surface-enhanced Raman scattering (SERS) and tip-enhanced Raman spectroscopy (TERS) address this limitation effectively [230, 231].

2.3.5. Nuclear magnetic resonance spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is an advanced characterisation technique widely employed for determining molecular structure of the majority of organic and inorganic compounds in solid, liquid, and gaseous states [232]. Offering both qualitative and quantitative insights, NMR spectroscopy provides valuable information on structural details and dynamic interactions at both intermolecular and intramolecular levels [233]. NMR's fundamental principle relies on nuclei possessing electric charge and spins, interacting with an external magnetic field to facilitate energy transfer, typically at radio frequencies [234, 235]. While NMR spectroscopy faces sensitivity limitations due to the relatively low energy scales involved, especially when compared to methods like fluorescence and UV-vis spectroscopy, which require smaller sample amounts [233, 236], advancements in the development of stronger magnets and more sensitive NMR probes [237], have effectively addressed these challenges. High-field nuclear magnetic resonance (HF-NMR) is certainly the most powerful and sophisticated spectroscopic technique but its integration with flow reactors is complicated by the cost and the size of NMR machines which are rarely installed close to a fume hood [238-241]. The launch of Low-field (LF) benchtop NMR spectrometers, based on rare-earth permanent magnets operating at a low magnetic field, has paved the way for reaction monitoring [242] and process control [243] in flow systems, significantly broadening the number of users, allowing for accurate quantification (below $\pm 1\%$) and complete molecular structure elucidation.

Monitoring chemical reactions in micromixers or microreactors requires minimal fluidic interconnection to minimize disruption between the micro-reactor and the NMR flow cell to minimize any adverse effects on the reaction [190–196]. Innovative designs, such as planar NMR microcoils and stripline configurations, enable localised detection within microchannels, providing enhanced resolution and straightforward integration onto microreactor chips for in situ analysis. Nonetheless, the usage of these integrated systems is constrained by their reliance on regular NMR systems for accommodating microfluidic chips or microreactors.

2.4. Development of automated systems for kinetic studies

The transition from conventional batch techniques to developing and implementing novel reaction systems in continuous flow or adapting traditional chemical transformations to this mode of operation is not a trivial endeavour. Unlike the simple process of dissolving or suspending reagents in a solvent, maintaining a constant temperature, and stirring until completion, continuous flow processes demand a higher level of technological sophistication and technical training. While the allure of automating continuous processes promises increased efficiency, reproducibility, and safety, automation itself is far from straightforward. It requires a continuous iterative approach involving ongoing scrutiny and refinement by both humans and machines. Within the realm of kinetic studies, three key components hold significance: the reactor system (including the incorporation of various instrument drivers, sensors, controllers and analytical techniques), the model identification software, and the interface between hardware and software, all of which are elaborated upon in the subsequent sections.

2.4.1. Hardware considerations

The initial phase in establishing an automated platform for kinetic studies involves identifying the essential hardware modules required to conduct an experimental cycle effectively. During the selection of system components, a delicate balance must be maintained between cost, development time and adaptability to variations in experimental protocols [244]. Challenges often arise concerning component limitations for specific tasks, compatibility issues among modules or with the chemistry involved, or system malfunctions due to inadequate coding. Academic laboratories often opt for constructing their own systems due to tighter budget constraints, the flexibility to explore multiple projects with slight modifications to the set up (plug-and-play units), and less restrictive timelines. In contrast, industrial laboratories typically prefer purchasing ready-made systems, offered by several companies, including Syrris, Tecan, Mettler-Toledo, Autichem, and Hamilton. While these systems come at a premium cost, they require minimal development efforts. Furthermore, the level of user automation and programming proficiency also plays a crucial role in the decision-making process between purchasing an integrated unit or assembling. In environments with expert users, custom platform construction may be more suitable, as the users possess the knowledge and skills to customise and optimise the system according to specific research needs. In settings with novice users, investing in commercial platforms equipped with user-friendly graphical interfaces and readily accessible technical support may be preferable. Although pipetting robots, such as the Andrew Alliance liquid handling robot [245], and robotic arms have gained

traction in facilitating high-throughput experiments and even executing scalable synthesis in automated platforms [246], they are considered out of scope for this study.

In Figure 2-7, various components assembling a continuous experimental set-up are depicted. As this thesis focuses on liquid-phase reagents, when operating in continuous mode, a fundamental component of the experimental rig is the liquid handling system. The liquid handling system includes the pumps for liquid displacement, valves for directing flow, and an assortment of tubes and connections to ensure leakage-free operation. Peristaltic pumps and syringe pumps are commonly observed in automated systems, each with distinct operating mechanisms and applications [247]. A peristaltic pump employs rotating rollers or shoes to compress flexible tubing, inducing a sequence of occlusions and relaxations that propel fluids through the tubing. Peristaltic pumps are cost-effective, suitable for a wide array of fluids including corrosive, viscous, and shear-sensitive substances, and can be utilized for continuous dispensing of larger volumes in the milliliter range. Conversely, syringe pumps operate via a motorised piston or screw mechanism to manipulate a plunger within a syringe barrel, ensuring precise delivery of fluid volumes. Equipped with distributive or non-distributive valves for flexible flow path planning, syringe pumps are renowned for their exceptional precision and accuracy in dispensing small fluid volumes in the microliter range [248].

Another critical component of an automated set-up is the temperature control system, essential for maintaining a constant and precise temperature within the reaction vessel. Temperature stability is paramount for ensuring the reproducibility and accuracy of kinetic measurements, as even slight fluctuations in temperature can significantly impact reaction rates and product yields. Achieving homogeneity of temperature throughout the reaction mixture is typically accomplished using circulator heating/cooling modules, which are readily available from companies like Huber. Alternatively, Peltier-based heating/cooling capabilities can be integrated into automated reactors, allowing for a greater number of zones with individual temperature control. In laboratories, a staple for heating are hot plates, capable of reaching working temperatures exceeding 600°C, depending on the material of the plate surface. Among the most widely used types of hot plates are those that combine powerful, microprocessor-controlled motors and magnets with uniform heating surfaces, known as hotplate stirrers that can be used in conjunction or separately [249].

When developing an automated platform for obtaining reaction kinetics, various auxiliary elements facilitating process monitoring are equally important to ensure the robustness and safety of the experimental setup. These elements serve as indicators, controllers (capable of providing feedback and regulating the instruments integrated into the platform) or safety

measures. Examples include temperature sensors, pressure sensors, mass flow meters and pressure relief valves [250].

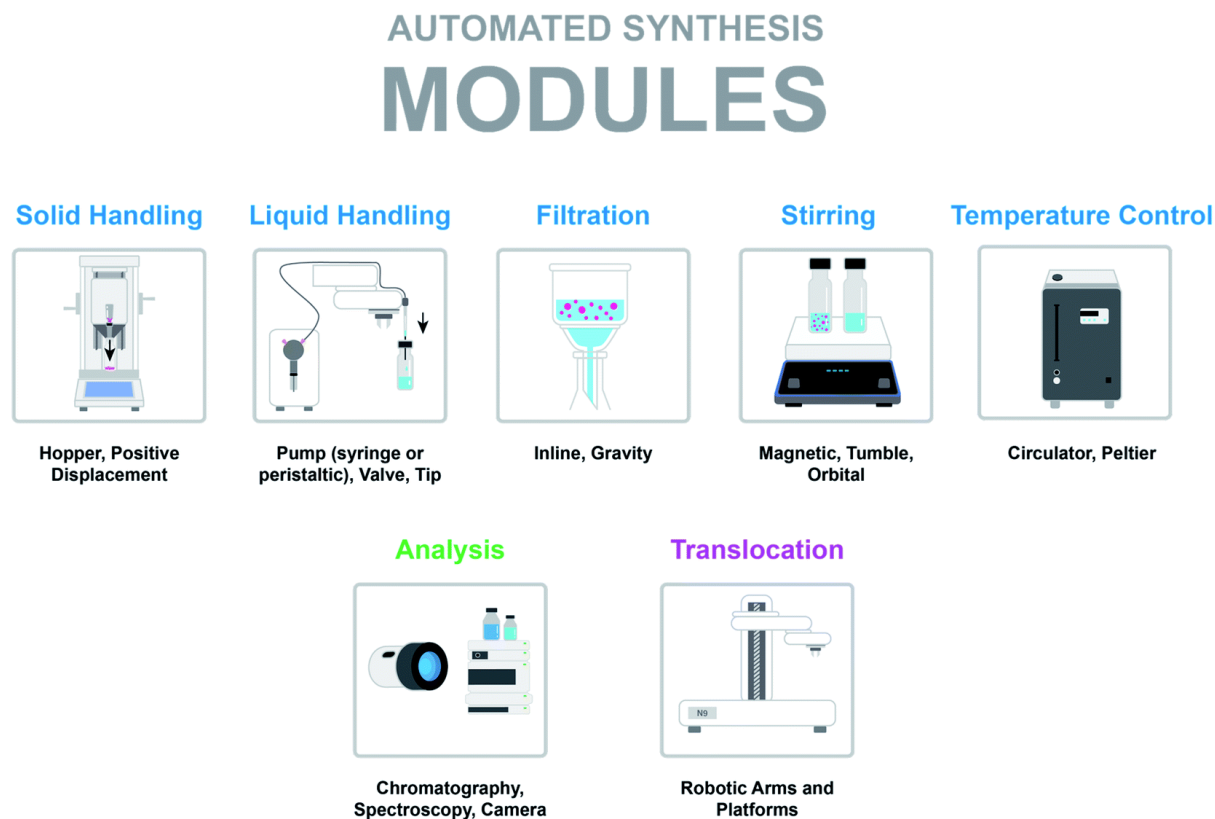


Figure 2-7. Instrumentation requirements for automated platforms (adapted from [161] under the Creative Commons Attribution-NonCommercial 3.0 Unported Licence).

The final component and arguably one of the most challenging modules to incorporate in an automated platform, is the analytical instrument used to provide quantitative and/or qualitative data for the investigated reaction inline. As explained in Section 2.2, multiple chromatographic and spectroscopic techniques have been employed with miniaturised reactors. The complexities associated with integrating analytics into a system primarily stem from the fact that most instruments available on the market are designed and sold as standalone systems, often incorporating their own automation technology, making them less adaptable to integration within a platform.

2.4.2. Model identification software for reaction kinetics

Optimisation algorithms for discrete and continuous variables, based on single or multi-objective functions, have demonstrated efficacy in rapidly optimising reaction conditions to enhance product yield, as well as chemo-, regio-, and/or stereo-selectivity. This has led to the emergence of closed-loop flow reactor systems, termed “self-optimising reactors” [58, 61, 62,

251-256]. By employing Design of Experiments (DoE) methods that require little prior knowledge of the system, this approach accelerates reaction screening and reduces experimental time and resources, however it may not necessarily offer a comprehensive, information-rich methodology directly applicable to any reaction system. Experiments are typically confined to the region surrounding the optimum operating point and may provide limited value for the development of a kinetic model that explores a wider design space and is suitable for scale-up purposes [65].

The development of a kinetic model involves identifying the most suitable model structure, comprising a set of kinetic rate equations, among alternative candidate models and precisely estimating its kinetic parameters to match the process response over the selected range of operating conditions [51]. Traditionally, model structures have been formulated on a physics-based description of the systems' dynamics, known as mechanistic models, and will be the focus of this thesis. However, it is worth mentioning that data-driven approaches utilising machine learning-assisted model development techniques are gaining traction. Automatic mechanism generation tools rely on accurate training data from experiments or quantum chemistry calculations and systematically enumerate and evaluate potential chemical pathways, thereby reducing the chance of human error and redundant tasks associated with scripting model equations [257].

In automated, continuous flow reactors, two predominant approaches (and their hybrid counterparts) have been widely adopted for kinetic studies. The first method relies on the design of experiments using pure statistical (model-free) DoE methods, such as Factorial DoE and Latin Hypercube Sampling (LHS) [70]. These type of DoE designs are straightforward to implement and measure the effect of input factors (and the interaction between them) on a response (output), thus providing the most information on the input-output relationship. This 'black-box' experiment design usually constitutes a preliminary screening study and is implemented in systems, where no prior information is available. Although they allow the screening of a wide design space and they are effective on reducing the expected variance of measurements [258], classic statistical design techniques do not necessarily guarantee highly informative experiments [16], prompting the utilisation of Model-Based Design of Experiments (MBDoE) techniques.

MBDoE techniques represent a consolidated tool for the rapid assessment and identification of fundamental kinetic models by optimally designing a set of experiments, yielding the maximum information content for model identification [16]. Using initial parameter guesses, either intuitively, from literature, or from screening experiments, MBDoE techniques facilitate the identification of the most suitable model between competing models (MBDoE for model

discrimination) [16, 65, 259, 260] and the improvement of parameter estimates of an already selected model (MBDoE for parameter precision) [261-263]. These methods have been successfully applied offline, where statistical tools are employed to analyse preliminary experimental data and derive a sequence of new, optimally designed experiments to be further conducted. The delays created by the time taken to run the experiments, perform model discrimination and update the parameter estimates can be improved when a feedback process is imbedded in the experimental platform. Online MBDoE experiments [16, 264] for reaction kinetics have been successfully reported in smart platforms [51, 69, 265], where DoE or MBDoE methodologies are employed for deciding on the initial experimental conditions. Each data set produced in an experimental cycle is analysed online upon completion, the results are used to calibrate the model, and based on the objective of the experiments (discrimination between most probable models or improving the precision of parameters of the most probable model) the algorithm decides on the next, optimal experimental condition [71].

Challenges related to ill-posed estimation of parameters after model discrimination can be addressed through online parametrisation, which serves as an effective and robust tool for the transformation of kinetic model parameter space during online model identification [266]. Multi-objective optimisation techniques for joint model-based design of experiments aim to deal with model discrimination and improvement of the kinetic parameters' estimation simultaneously, maximising experimental data acquisition from minimal experimentation [261]. Furthermore, the application of ML techniques, particularly artificial neural networks (ANNs), as regressors [267-270] or classifiers [271, 272] for kinetic modelling, has gained interest. The combination of ANN-based kinetic model recognition methods with optimal design of experiments represents a novel class of DoE frameworks, similar to MBDoE procedures, but with distinction in how the optimisation problem is defined and numerically solved [273].

2.4.3. Software and hardware interface

The data flow between the various components within an automated experimentation framework is thoroughly presented in the work of Flores-Leonar et al. [274] and Bai et al. [2] (Figure 2-8). In the context of this thesis, the interaction between software and hardware interfaces focuses on two core aspects: firstly, the ability of selected hardware to execute designated tasks contingent upon software or firmware control accessibility, and secondly, the communication between model identification software and hardware units to determine and enact subsequent experimental conditions, particularly in autonomous systems.

In practical applications, disparate software solutions often govern individual instruments or hardware components, emphasizing the significance of Application Programming Interfaces (APIs) [275]. The functionality of software controlling desired hardware largely determines its

effectiveness within an automated workflow. Integration becomes streamlined with well-documented APIs, while their absence necessitates custom script development or resorting to hardware workarounds. A notable automation software offering a user-friendly human-machine interface for workflow management is Laboratory Virtual Instrument Engineering Workbench (LabVIEW) [276].

LabVIEW is a graphical programming environment created by National Instruments. Instead of traditional text-based coding, LabVIEW uses a graphical programming language called G (Graphical Programming Language), where commands are drawn as flowsheets with logic and loop structures [276]. LabVIEW has garnered extensive attention in laboratory environments for building automated and autonomous platforms [10, 51, 69, 70, 277, 278], primarily through the ease of integration of various component drivers (especially those developed by National Instruments) and its compatibility with Python and MATLAB coded optimisation scripts (such as those described in Section 2.3.2). Supported by a vibrant community and extensive documentation, LabVIEW is accessible to users of all skill levels and available across multiple platforms, ensuring flexibility and interoperability in diverse environments [279].

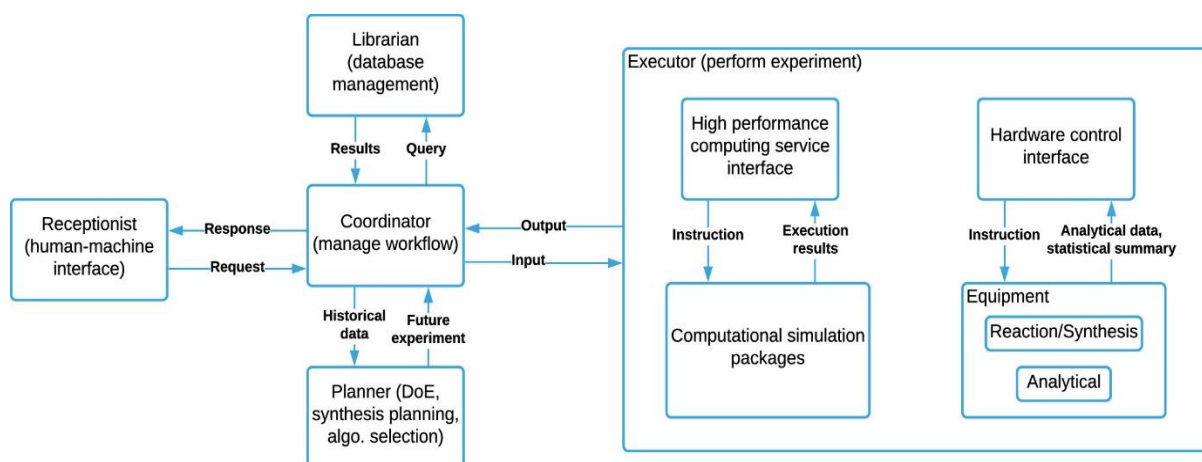


Figure 2-8. Functional elements of a platform-oriented strategy for chemical exploration and their respective interconnections (adapted from [2] under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International Licence).

Chapter 3. Modelling of hydrodynamics and liquid-to-particle mass transfer in a Single Pellet String Reactor

3.1. Introduction

The development and study of new catalysts and the optimisation of existing catalytic systems require efficient laboratory-scale experimentation. Integral to this process is the elucidation of reaction kinetics, a critical component for process design, operation, and control. To obtain the reaction kinetics for catalytic systems, laboratory-scale reactors should work under the same conditions and process variables as industrial ones [280]. To use these data for scale-up, it is necessary to guarantee that the reported reaction kinetics are not masked by external mass transfer limitations [281]. However, laboratory-scale reactors often exhibit disparities in hydrodynamics compared to their industrial counterparts due to lower superficial velocities and different flow patterns [282]. Consequently, these differences may lead to reduced mass transfer, limiting reaction rates and yields, thereby complicating the scalability of experimental data.

In the 1960s, a solution to these challenges emerged with the introduction of Single Pellet String Reactors (SPSRs) [283], where catalytic particles were packed into reactor structures of slightly larger diameter than the particles' diameter. Characterised by a small aspect ratio, δ , defined as the ratio of the reactor hydraulic diameter over the particle diameter, typically ranging between 1 and 5 [284], SPSRs enable the use of similar superficial velocities as industrial scale reactors, ensuring plug flow behaviour with minimal bypass and channelling, as the fluid is forced to flow over the catalyst particles [285-287]. Advantages, also, include the reproducibility of packing [288] and the use of industrial sized catalyst pellets (commercial catalyst extrudates in their original form are preferred to powder), the latter allowing the catalyst pellet skin effects to be investigated [289]. Despite the demonstrated advantages of SPSRs for studying reaction kinetics, literature on external mass transfer in these reactors remains limited compared to traditional packed bed reactors [290].

The investigation of average volumetric liquid-solid external mass transfer commonly involves experimental techniques, such as the diffusion-controlled dissolution of copper particles and the physical dissolution of active organic particles. Tidona et al. [291] conducted a study on liquid-to-particle mass transfer effects in rectangular and circular horizontal micro-packed beds containing copper particles ranging in diameter from 320 μm to 1.98 mm and aspect ratios from 2.4 to 24.4, using the copper dissolution technique. Employing the same methodology, Templis and Papayannakos [288] investigated the liquid-to-particle mass transfer effects in a string pellet minireactor with an aspect ratio of 1.33, filled with cylindrical particles of 1.5 mm in spiral and vertical configurations, operating with liquid and gas-liquid feeds. Similarly, Waldron et al. [69] used a string of 3 and 10 copper beads of 947 μm in reactors with aspect ratio equal to 1.06 and 1.68, in an effort to guarantee that the reaction

kinetics of benzoic acid esterification in a SPSR were not subject to external mass transfer limitations. Experimental results for the mass transfer between spherical naphthalene particles with average diameters of 1.06, 2.02 and 2.83 mm and air in packed tubes of very low tube-to-particle diameter ratio ($\delta = 1.41, 1.98, \text{ and } 3.7$ respectively), were presented by Tsotsas and Schlünder [292], whilst Hipolito [293] determined liquid-to-particle mass transfer coefficients by dissolving 2 mm and 4 mm spherical particles of b-naphthol in organic effluent for single- and two-phase flow experiments in a horizontal square-shaped string reactor, resulting in mean aspect ratios of 1.1 and 1.7. Romkes et al. [294] obtained the experimental mass transfer coefficient for gas systems by determining the rate of mass decrease of 12.7 mm naphthalene spheres at constant gas velocity in a composite square duct reactor of aspect ratio smaller than 2. In all these works, the mass transfer coefficient was expressed in terms of Sherwood number (Sh) as a function of Reynolds number (Re) and Schmidt number (Sc) and relevant empirical correlations were developed.

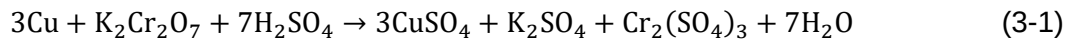
Romkes et al. [294] and Templis and Papayannakos [288] incorporated an integrated approach, comparing experimental data with Computational Fluid Dynamics (CFD) modelling. Following this approach, Da Silva Pinho's study [295] exclusively relied on computational modelling for the investigation of hydrodynamics and liquid-solid mass transfer of a SPSR with spherical particles of 2.45 mm and an aspect ratio of $\delta = 1.25$, which operated at supercritical conditions, for the selective hydrogenation of MAPD to propylene. This holistic methodology provides a comprehensive understanding of hydrodynamics and mass transfer inside a reactor. The solutions generated through CFD modelling contain local values of relevant variables that are often challenging to define experimentally. Through the modelling of hydrodynamics and transport phenomena in SPSRs, as examined in this study, not only are experimental time and resources conserved, but it also becomes feasible to derive simple correlations for external mass transfer suitable for design purposes. This alternative to experimental work proves to be valuable, offering nuanced insight into the intricate dynamics of reactor systems.

Taking the above into consideration and given the inherent characteristics of the systems employed in this thesis, a CFD model for the investigation of the hydrodynamics and liquid to solid mass transfer in SPSRs, featuring cylindrical channels packed with spherical particles of average diameter of 947 μm and aspect ratios spanning between 1.06 and 1.68, is developed for flow conditions within the laminar regime. To ensure the robustness of the model, it is validated against experimental data obtained from the copper dissolution technique conducted by Waldron et al [69]. Two different approaches of post-processing the model's results for the calculation of the external mass transfer coefficient are pursued. Firstly, a macroscopic approach is implemented, involving the calculation of an average mass transfer coefficient,

grounded in the steady-state material balance of potassium dichromate along a packed bed. Secondly, a microscopic approach is adopted that allows for the estimation of local mass transfer around the spheres and along the reactor length. The results derived from these two approaches are subjected to a comprehensive comparative analysis, which also includes a thorough review of existing literature. The analysis culminates in the extraction of a global correlation for mass transfer evaluation that incorporates the most important SPSR parameter, the aspect ratio, δ , and not only enhances the understanding of the intricate dynamics within these systems, but also provides a valuable tool for predicting and improving their performance.

3.2. Modelling methodology

The simulations were based on the copper dissolution in an acidified dichromate solution [69, 288, 291], the overall reaction stoichiometry of which is presented in Equation 3-1. The reaction of the copper dissolution is considered instantaneous. Therefore, the rate-determining step is the diffusion of the chromate ion $\text{Cr}_2\text{O}_7^{2-}$ from the liquid bulk through the diffusion layer to the copper surface.



Since the investigation of internal mass transfer is out of the scope of this study, simulations focused exclusively on the fluid phase. The modelling of the solid copper spheres was achieved through meshing and by treating it as a wall surface, where no slip boundary conditions were applied. The mesh generation, flow simulation and transport of species were performed using COMSOL Multiphysics® v. 6.1 on a DELL OptiPlex 7060 Windows operated PC with Intel Core i7-8700 CPU and 16 GB of RAM. For model robustness, the segregated approach, where the unknown variables of the 3D model are solved sequentially within a single iteration was followed [296]. The model converged with a relative tolerance of $1\text{e-}3$.

3.2.1. Reactor geometry

Under ideal conditions, spherical particles in a SPSR are stacked in direct contact with each other, while simultaneously making alternating contact with the reactor walls, as shown in Figure 3-1. Therefore, the position of spherical particles within a SPSR with a cylindrical confining wall is mathematically defined as a function of the particle diameter, d_p (m), and the cylinder diameter D (m), based on trigonometric principles [297], as elaborated in Figure 3-1. The centre point coordinates of the i^{th} particle in a horizontal tube are given by Equations 3-2 to 3-4.

$$x = \frac{d_p}{2} + (i-1) \cdot \sqrt{d_p^2 - (D-d_p)^2} \quad (3-2)$$

$$y = (-1)^i \cdot \frac{D-d_p}{2} \quad (3-3)$$

$$z = 0 \quad (3-4)$$

The reactor length, L_{reactor} (m) is determined by Equation 3-5 [297].

$$L_{\text{reactor}} = d_p + (N_{\text{particle}} - 1) \cdot \sqrt{d_p^2 - (D-d_p)^2} + (-1)^i \cdot \frac{D-d_p}{2} \quad (3-5)$$

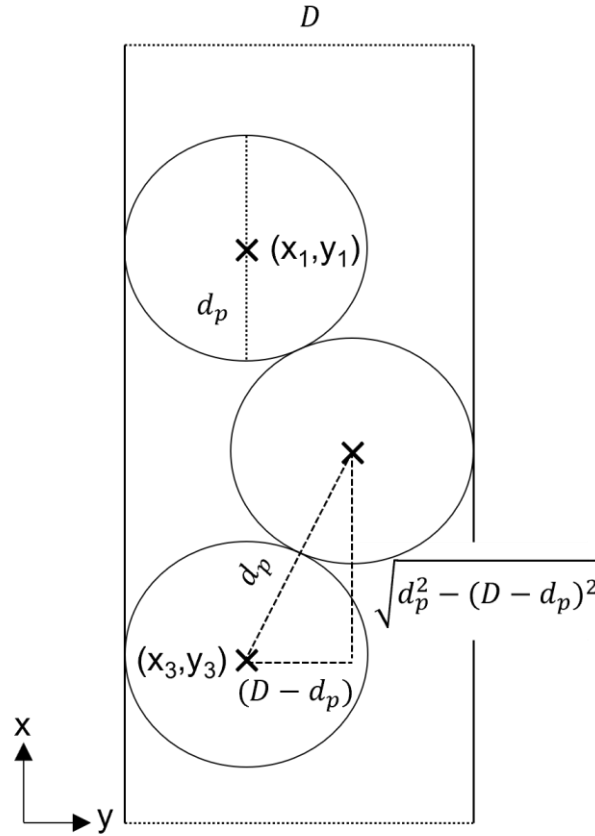


Figure 3-1. Cross section of a SPSR showing the trigonometric expressions used for the analytical particle position.

An important parameter of the SPSR is the aspect ratio, δ , defined as the ratio of the reactor diameter over the diameter of the particle (Equation 3-6).

$$\delta = \frac{D}{d_p} \quad (3-6)$$

Although dissolution techniques modify the surface area of the particles and consequently their size [298, 299], for simplification purposes, the copper particles simulated were considered of constant diameter.

3.2.2. Mesh generation

The quality of the mesh is crucial for a finite element simulation, as it enables the derivation of precise solutions using a reduced element count, while maintaining reasonable computational efficiency. The mesh generation interface of COMSOL Multiphysics® v. 6.1 offers the capability to generate meshes of varying densities, tailored to user specifications. In this case, opting for physics-controlled meshing fine-tuned for fluid dynamics, resulted in the creation of an unstructured tetrahedral grid that effectively discretised the computational domain. The mesh generation process commenced with cell refinement near particle surfaces within the background mesh, coupled with the removal of cells encompassing the particles. Localised refinements were applied to solid surfaces and small gaps, followed by corner refinements, designed to decrease the element size at sharp corners. To capture boundary layers, layers of mesh cells were introduced in proximity to the walls and particle surfaces. The remaining unmeshed geometry was meshed using tetrahedral cells. The resulting mesh predominantly featured tetrahedral elements, with the inclusion of prismatic cells near the walls and pyramid-shaped cells at the contact points of spheres-spheres and spheres-walls. A comprehensive examination of mesh convergence is presented in Section 3.3 of this thesis. Due to the complicated nature of the reactor's geometry, the generated mesh contained elements of lower quality in the areas of contact points between the solids (particle-particle, particle-wall), where the fluid elements became highly skewed, meaning that some of their surfaces were much larger than others within the same tetrahedron. However, this skewed mesh around the contact points did not create any problems for laminar solutions concerning model convergence. Details of the mesh in these areas and comparison of this methodology with the approaches of the so-called 'shrink' factor or 'near-miss' model (introduced by Calis et al. [290] and Nijemeisland and Dixon [300], respectively), where all particles were shrunk by 1% of the diameter after the initial definition of the bed to avoid the generation of low-quality elements, are presented in Appendix A.

3.2.3. Hydrodynamic model

The simulated copper dissolution reaction was considered to occur under isothermal and isochoric conditions over non-porous spherical particles, at ambient temperature (20 °C). The dichromate anion solution was represented as a viscous and incompressible Newtonian fluid within a three-dimensional domain. The solid particles were held stationary, and the interstitial space between them remained constant throughout. All simulations were conducted under the laminar flow regime, with Reynolds number ranging from 5 to 100 [15]. The Reynolds number was defined based on the equivalent diameter of the SPSR, that takes into consideration the effect of the confining walls (Equation 3-7, 3-8 and 3-9).

$$Re_h = \frac{\rho u_{int} d_h}{\mu_L} \quad (3-7)$$

$$u_{int} = \frac{u_0}{\varepsilon} = \frac{Q_0}{A_0 \varepsilon} \quad (3-8)$$

$$d_h = \frac{6 \cdot V_p}{S_p + f_w S_w} \quad (3-9)$$

Where ρ is the fluid density (kg/m³), u_{int} is the average interstitial velocity (m/s), d_h is the hydraulic diameter (m), μ_L is the dynamic viscosity (Pa·s), u_0 is the superficial velocity (m/s), Q_0 is the inlet flowrate (m³/s), A_0 is the empty cross-section of the channel (m), ε is the reactor's porosity (calculated based on the correlations proposed by Dixon [301]), V_p is the total volume of particles (m³), S_p is the total surface of particles (m²), S_w is the wall surface (m²) and f_w is a weighting factor (calculated based on the empirical equation proposed by Fernengel et al. [302] to scale the influence of the confining wall). The procedure followed for the calculation of these parameters, as well as their respective values for each simulated configuration, can be found in Appendix A.

Consequently, the laminar flow through the void volume of the reactor was described by solving the steady-state incompressible Navier-Stokes equations, as defined in Equations 3-10 and 3-11. Equation 3-10 describes the conservation of momentum and Equation 3-11 is the continuity equation.

$$\rho(\mathbf{u} \cdot \nabla)\mathbf{u} = \nabla(-P\mathbf{I} + \boldsymbol{\tau}) + \mathbf{F} \quad (3-10)$$

$$\rho \nabla \cdot \mathbf{u} = 0 \quad (3-11)$$

Where, $\mathbf{u}$ is the velocity vector (m/s), P is the pressure (Pa), $\mathbf{I}$ is the identity matrix, $\boldsymbol{\tau}$ is the viscous stress tensor (Pa) and $\mathbf{F}$ represents the external body forces that act on the fluid (N/m³). Due to the reactor simulated horizontally, gravity was not included in the simulations and since no other external forces were exerted on the fluid, $\mathbf{F}=0$.

The flow was set as fully developed at the reactor inlet (Equation 3-12), which prescribes that the tangential flow component on the boundary is zero.

$$\mathbf{u} \cdot \mathbf{t} = 0 \quad (3-12)$$

Where, $\mathbf{t}$ is the tangential unit vector.

No-slip boundary conditions (Equation 3-13) were applied at the reactor's walls and the external surface of the catalytic particles.

$$\mathbf{u} = 0 \quad (3-13)$$

3.2.4. Mass transfer model

Convection and diffusion under steady state according to Fick's law was used to describe the transport of the dichromate ion, as presented in Equation 3-14.

$$\frac{\partial c}{\partial t} + \nabla \cdot (-D_m \nabla c) + \mathbf{u} \cdot \nabla c = 0 \quad (3-14)$$

Where, D_m is the molecular diffusion coefficient of the chemical component (m^2/s) and c is the component concentration (mol/m^3).

Considering the dichromate ion reduction on the surface of the non-porous copper particles as instantaneous, the heterogeneous reaction can be introduced as a boundary condition of zero dichromate ion concentration on the surface of the copper particles, c_s (mol/m^3) (Equation 3-15).

$$c_s = 0 \quad (3-15)$$

The physical properties of the dichromate anion solution are presented in Table 3-1.

Table 3-1. Physical properties of the dichromate anion solution at ambient temperature [291].

ρ (kg/m^3)	μ_L ($\text{Pa}\cdot\text{s}$)	D_m (m^2/s)
1068	0.001007	1.375e-9

3.2.5. External mass transfer coefficient evaluation

External mass transfer coefficients can be estimated through correlations involving dimensionless numbers, primarily Sherwood (Sh), Reynolds (Re), and Schmidt (Sc) numbers. Specifically, for monophasic laminar flow, the liquid-to-solid mass transfer within packed bed reactors [303] and SPSRs [282, 288] can be expressed as follows:

$$\text{Sh} = 2 + c_1 \text{Re}^{c_2} \text{Sc}^{c_3} \quad (3-16)$$

$$\text{Sh} = \frac{k_{LS} d_p}{D_m} \quad (3-17)$$

$$\text{Sc} = \frac{\nu}{D_m} \quad (3-18)$$

Where, c_1 , c_2 and c_3 are dimensionless constants, k_{LS} is the liquid-to-solid mass transfer coefficient (m/s) and ν is the kinematic viscosity (m^2/s). Notably, in the case of spherical particles, literature suggests that c_3 is equal to $1/3$ [304]. Therefore, for spherical particles, variation of the Reynolds number alone is adequate to estimate the mass transfer correlation for the investigated reactor configuration. In this work, the liquid-to-solid k_{LS} mass transfer coefficient was directly post-processed, following the computation of dichromate anion concentration. Two distinct approaches were employed for the calculation of the external mass transfer coefficient: a macroscale approach and a microscale approach, both based on the same model results but differentiating in terms of post-treatment. The detailed methodology for each approach is elucidated in the following subsections.

The Sherwood number values, computed in this work, were compared to existing correlations for packed beds and SPSRs, as presented in Table 3-2. In Table 3-2, Re_0 refers to the Reynolds number calculated based on the particle diameter, d_p and the superficial velocity, u_0 , and Re_{int} is the Reynolds number calculated based on the particle diameter, d_p and the interstitial velocity, u_{int} . A summary of the correlations for the estimation of external mass transfer in terms of Sh is presented in Figure 3-2 for Re up to 100.

Table 3-2. Available correlations for the estimation the external mass transfer in packed beds and SPSRs based on experimental and CFD studies for a range of Reynolds numbers.

Authors	Fluid phase	Correlation	Description	Reynolds number	Study type
Wakao and Funazkri (1978) [305]	Gas and liquid	$Sh_{Wa} = 2 + 1.1Re_0^{0.6}Sc^{\frac{1}{3}}$	Packed bed with fixed porosity, $\varepsilon = 0.4$	$3 < Re_0 < 10000$	Experimental
Gnielinski (1981) [306]	Gas	$Sh_{Gn} = f_\varepsilon \cdot [2 + \sqrt{Sh_1^2 + Sh_2^2}]$ With $Sh_1 = 0.664Re_{int}^{\frac{1}{2}}Sc^{\frac{1}{3}}$ $Sh_2 = \frac{0.037 Re_{int}^{0.8}Sc}{1 + 2.443 Re_{int}^{-0.1}(Sc^{\frac{2}{3}} - 1)}$ and $f_\varepsilon = 1 + 1.5(1 - \varepsilon)$	Packed bed of equally-sized spheres for $0.26 < \varepsilon < 0.935$.	$Re_{int} < 2 \cdot 10^4$	Experimental
Hipolito (2010) [293]	Liquid	$Sh_{Hi} = 2 + 0.7Re_0^{0.5}Sc^{\frac{1}{3}}$	Square-duct SPSR with spherical particles ($2 < d_p < 2.83$ mm and $3.15 < d_p < 4$ mm)	$0 < Re_0 < 350$	Experimental

			mm, w x h=4 x 4 mm ² , 1< δ <2)		
Da Silva Pinho (2015) [295]	Liquid	Sh_{DS} $= 2 + 1.202Re_0^{0.574}Sc^{\frac{1}{3}}$	Circular-duct SPSR with spherical particles (2.38< d_p <2.5 mm, D=3 mm, 1.06< δ <1.2)	0< Re_0 <200	CFD
Romkes et al (2003) [294]	Gas	Sh_{Ro} $= 1.06 + 0.796Re_h^{0.621}Sc^{\frac{1}{3}}$	Rectangular-duct SPSR with spherical particles (d_p =12.7 mm, 12.7< w x h <26 mm ² , 1< δ <2)	$1.27 \cdot 10^{-4} < Re_h < 1.27 \cdot 10^5$	CFD
Templis and Papayannakos (2017) [288]	Liquid	Sh_{Te} $= 2.06$ $+ 0.3816Re_0^{0.614}Sc^{\frac{1}{3}}$	Circular-duct SPSR with cylindrical particles (d_p =1.5 mm, D=2 mm, δ =1.33)	0.59< Re_0 <11.63	Experimental
Tidona et al. (2013) [291]	Liquid	Sh_{Ti} $= 2 + 1.96Re_0^{0.53}Sc^{0.26}$	Rectangular-duct packed bed with spherical particles (d_p =149 μ m, w x h= 400 x 360 μ m ² , δ =2.5)	0< Re_0 <80	Experimental

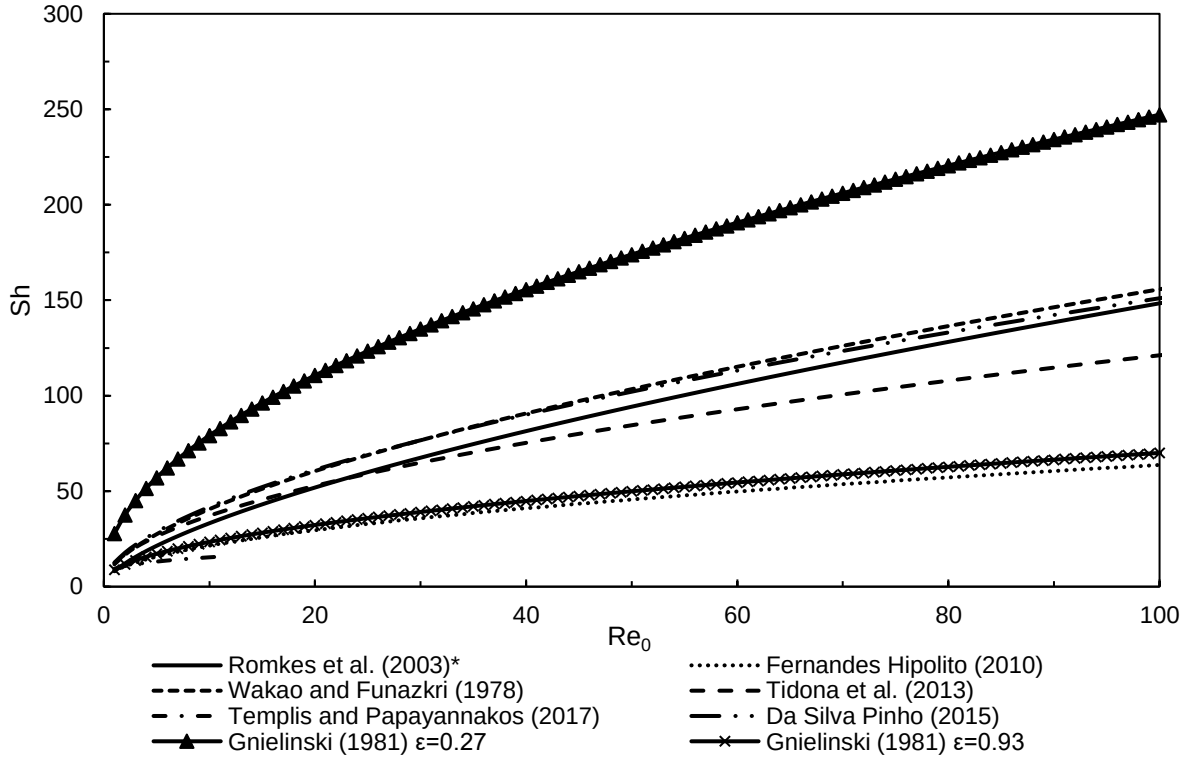


Figure 3-2. Sh vs Re_0 for proposed literature correlations for $Re_0 \leq 100$. The asterisk (*) indicates correlations where Re_h was used in place of Re_0 due to unavailability of data for direct comparison.

3.2.5.1. Macroscale approach

The macroscale approach, as suggested by its name, is an average representation of the microscopic process [307] and focuses on describing and analysing the overall mass transfer coefficient in a SPSR by conceptualizing the reactor as a holistic entity. The approach employs well-established mathematical equations to describe both the mass transfer of dichromate anions from the bulk liquid to the solid surface and the reaction occurring on the external surface of the copper particles. The macroscale approach is based on the steady-state material balance of potassium dichromate along the reactor bed, assuming uniform flow distribution over the cross-section, as presented in Equation 3-19.

$$D_{ax} \frac{\partial^2 c(x)}{\partial x^2} - u_x \frac{\partial c(x)}{\partial x} - k_{LS} \alpha c(x) = 0 \quad (3-19)$$

Where, D_{ax} is the axial dispersion coefficient (m^2/s), u_x is the velocity in the x-direction (main flow direction, m/s), and α is the surface area of the copper particle per unit reactor volume (m^2/m^3). To simplify the calculations, the value of u_x was considered constant and equal to the inlet superficial velocity, u_0 .

Applying the Danckwerts boundary conditions at the inlet (Equation 3-20) and the outlet (Equation 3-21) of the SPSR, Equation 3-19 transforms into Equation 3-22 [104].

$$\text{At } y=0, u_0(c_0 - c(x)) = -D_{ax} \frac{dc(x)}{dx} \quad (3-20)$$

$$\text{At } y=L_{\text{reactor}}, \frac{dc(x)}{dx} = 0 \quad (3-21)$$

$$\frac{c_{\text{outlet}}}{c_0} = \frac{4B \cdot \exp\left(\frac{u_0 \cdot L_{\text{reactor}}}{2 \cdot D_{ax}}\right)}{(1+B)^2 \cdot \exp\left(\frac{B \cdot u_0 \cdot L_{\text{reactor}}}{2 \cdot D_{ax}}\right) - (1-B)^2 \cdot \exp\left(-\frac{B \cdot u_0 \cdot L_{\text{reactor}}}{2 \cdot D_{ax}}\right)} \quad (3-22)$$

Where B is expressed as in Equation 3-23.

$$B = \sqrt{1 + \frac{4 \cdot k_{LS} \alpha \cdot D_{ax}}{u_0^2}} \quad (3-23)$$

The specific surface area α is calculated by Equation 3-24.

$$\alpha = \frac{4 \cdot S_p}{L_{\text{reactor}} \cdot D^2 \cdot \pi} \quad (3-24)$$

In Equations 3-20 to 3-24, c_0 is the inlet concentration of dichromate solution (mol/m³) and c_{outlet} is the outlet concentration (mol/m³). To solve the Equation 3-22 and obtain the liquid-to-solid mass transfer coefficient, k_{LS} , the outlet concentration, c_{outlet} , as well as the axial dispersion coefficient D_{ax} , need to be estimated. The CFD predicted average bulk concentration at the outlet of the reactor can be directly calculated as the cup-mixing concentration $c_{\text{outlet}}(x)$ [308], according to Equation 3-25.

$$c_{\text{outlet}}(x) = \frac{\iint_{A_{\text{int}}} c(x, y, z) \cdot u_x(z, y) dy dz}{\iint_{A_{\text{int}}} u_x(z, y) dy dz} \quad (3-25)$$

Where, $u_x(z, y)$ (m/s) is the axial velocity as a function of position (y,z) in the cross section, and the integrals are taken over the cross section of the channel A_{int} (m²). For the calculation of the axial dispersion coefficient, simulations of the residence time behaviour were conducted.

If one considers a plug flow reactor model (i.e, if axial dispersion is neglected), Equation 3-19 can be simplified as:

$$u_0 \frac{\partial c(x)}{\partial x} - k_{LS} \alpha c(x) = 0 \quad (3-26)$$

The integration of Equation 3-26 gives Equation 3-27.

$$k_{LS}\alpha = -\frac{u_0}{L_{\text{reactor}}} \ln \left(\frac{c_{\text{outlet}}}{c_0} \right) \quad (3-27)$$

3.2.5.1.1. Calculation of axial dispersion

The Residence Time Distribution (RTD) along the string of particles was assessed through a numerical tracer pulse experiment, following a methodology similar to that used by Müller et al. [309]. The transient transport of a passive tracer species through the SPSR, accounting for both convection and diffusion effects, was considered. To model a tracer pulse, c_{tracer} (mol/m³) for the studied residence time, a time-dependent concentration function was implemented at the reactor inlet when solving the mass transfer model of Section 3.2.4 (Equation 3-28).

$$c_{\text{tracer}}(t) = c_{\text{tracer},0} \cdot e^{-(t-3)^2} \quad (3-28)$$

The axial dispersion model, as mathematically delineated by Equation 3-29, describing the hydrodynamics single phase flow in semi-infinite packed beds [310] and SPSRs with small values of δ and $\frac{L_{\text{reactor}}}{D} < 20$ [311] was employed.

$$D_{\text{ax}} \frac{\partial^2 c(x)}{\partial x^2} - u_0 \frac{\partial c(x)}{\partial x} = \frac{\partial c(x)}{\partial t} \quad (3-29)$$

The numerical set-up to determine the RTD that was used in this study, corresponded to an open-open configuration. Due to the limited length of the modelled bed, large deviation from plug flow was expected, as presented in Equation 3-30.

$$\frac{D_{\text{ax}}}{u_0 L_{\text{reactor}}} > 0.01 \quad (3-30)$$

Therefore, the cumulative distribution function of residence time, $E(t)$, can be described as [104]:

$$E(t) = \frac{u_0}{\sqrt{4\pi D_{\text{ax}} t}} e^{-\frac{(L_{\text{reactor}} - u_0 t)^2}{4D_{\text{ax}} t}} \quad (3-31)$$

By fitting the evaluated $E(t)$, right before the first and strictly after the last simulated particle, the axial dispersion coefficient D_{ax} , was determined. In the present work, the radial dispersion was not evaluated. In the context of flow through beds, it is a common empirical observation that the dispersion coefficient in the longitudinal direction tends to be approximately five times greater than the dispersion coefficient in the radial direction for Reynolds numbers exceeding

10 [312]. Consequently, under the studied conditions, the radial dispersion coefficient was assumed negligible.

To investigate the impact of axial dispersion on the calculation of the mass transfer coefficient and compare the CFD-calculated value for a SPSR with correlations for axial dispersion in packed beds, a proposed correlation by Rastegar and Gu [313] for liquid flow in packed beds with spherical particles – a system with liquid flow characteristics and beads shape resembling those of the SPSRs investigated in this thesis – was employed. The correlation incorporates both molecular diffusion and the porosity of the bed (Equation 3-32).

$$D_{ax} = 0.7D_m + \frac{d_p u_{int} \epsilon}{0.18 + 0.008 Re_0^{0.59}} \quad (3-32)$$

3.2.5.2. Microscale approach

The concept of a thin hypothetical stagnant film surrounding a particle, which accounts for all the mass transfer resistance at the interface of the bulk fluid and the solid particles, can be used to model diffusive transport to a surface [90]. The liquid-solid mass transfer coefficient, k_{LS} , is a function of the molecular diffusion coefficient, D_m , and thickness of the boundary layer outside the catalytic pellets, δ_{film} , as shown in Equation 3-33.

$$k_{LS} = \frac{D_m}{\delta_{film}} \quad (3-33)$$

The microscale approach, in contrast to the macroscale methodology that treats the reactor as an entity, seeks to assess the local molar flux between the bulk fluid (defined as the region far from the particle surface where the concentration is considered uniform) and the particle surface. The rationale behind adopting this approach stems from the intricate geometry inherent in SPSRs, where hydrodynamics and mass transfer are expected to exhibit a pronounced dependence on the aspect ratio, δ . Owing to the confinement imposed by the reactor walls, distinct zones with varying molar fluxes are present around each spherical particle. Therefore, the stagnant film model assumption of a uniform bulk liquid concentration is not a verified hypothesis for string pellet reactors [314].

To quantify the molar flux (normal to the sphere surface) at different distances around the particles and considering that simulations were conducted in Cartesian coordinates, the conversion to radial coordinates involved the creation of concentric spheres around the particles post-run and the subsequent update of the solution. The radii of these concentric spheres extended from the centre of each particle outward to the surrounding bulk fluid in distances of 3 μm (smallest possible distance based on the minimum element size of the grid), 5 μm , 10 μm , 20 μm , 35 μm , 50 μm , 60 μm , 80 μm and 100 μm away from the external particle

surface, as illustrated in Figure 3-3a, Figure 3-3b and Figure 3-3c. Each sphere was discretised into 16 equally divided surfaces, referred to as ‘crescent section’, as proposed in the work of da Silva [315] and the flux was evaluated at each surface. The detailed choice of the number of surfaces is provided in Appendix A.

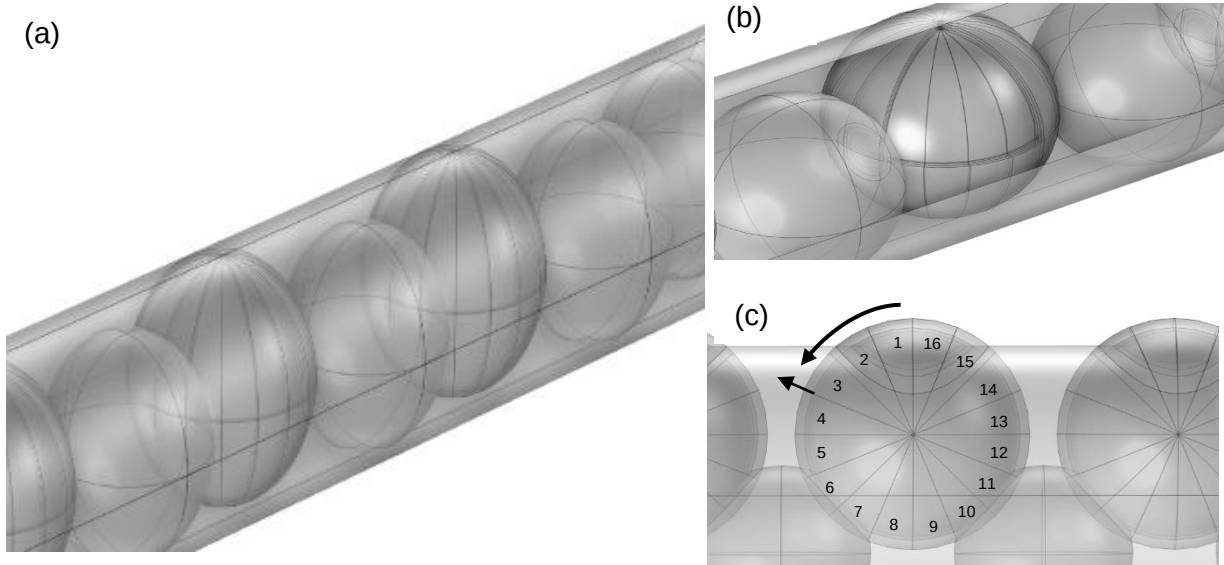


Figure 3-3. (a) 3D representation of concentric spheres for estimation of the local mass transfer coefficient in a SPSR, (b) Zoomed-in representation of the crescent sections extending radially from the catalyst surface to the bulk fluid and (c) Discretisation of each concentric sphere into 16 crescent sections (and subsequent angles). The two arrows represent the two directions of analysis: around the sphere and extending radially from the particle surface to the bulk liquid.

Equation 3-34 serves as the basis for estimating the local molar flux (normal to the sphere's surface), φ_θ ($\text{mol}\cdot\text{m}^{-2}\cdot\text{s}^{-1}$).

$$\varphi_\theta = -D_m \left. \frac{\partial c}{\partial r} \right|_{r=0,\theta} \quad (3-34)$$

Here, r denotes the radial position relative to the particle surface (m) and the index θ signifies the range of angles under analysis ($^\circ$). Assuming that the concentration gradient from the bulk liquid, $c_{b,\theta}$ to the catalyst surface, $c_{s,\theta}$, is linear within the thin film (Figure 3-4), the local flux φ_θ was calculated by identifying the region of linearity and fitting a straight line, the slope of which approximated the term $\left. \frac{\partial c}{\partial r} \right|_{r=0,\theta}$ of Equation 3-34.

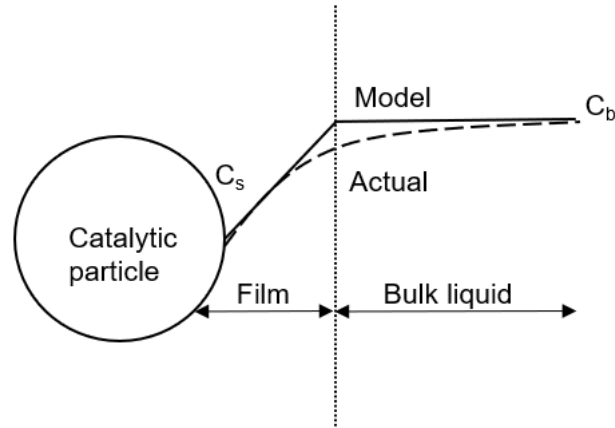


Figure 3-4. Film theory model of liquid-solid mass transfer assuming the concentration change from the bulk liquid (c_b) to the particle surface (c_s) is linear within a thin film.

After defining the local flux, φ_θ , the mass transfer coefficient at a specific θ angle, $k_{LS,\theta}$ was calculated based on Equation 3-35.

$$k_{LS,\theta} = \frac{\varphi_\theta}{(c_{b,\theta} - c_{s,\theta})} \quad (3-35)$$

Where $c_{b,\theta}$ is the bulk concentration (mol/m^3) of each crescent section at a specific angle.

Consequently, the overall mass transfer coefficient, k_{LS} , can be considered the average of the local mass transfer coefficients, as presented in Equation 3-36.

$$k_{LS} = \frac{\sum_{\theta=1}^{16} k_{LS,\theta}}{16} \quad (3-36)$$

The process of transforming the spatial coordinate system from Cartesian to radial coordinates using COMSOL Multiphysics® v. 6.1 introduced a minor interpolation error in the model results, amounting to 0.12%. This value was sufficiently small to be assumed negligible.

3.3. Set-up & boundary conditions

Four different geometries of a SPSR, each featuring a circular cross-section and filled with arrays of 10-13 particles, were simulated. These geometric variations were determined based on the channel-to-particle-diameter ratio, aiming to achieve similar reactor bed lengths. The basis for these SPSR configurations stemmed from existing experimental data of the copper dissolution reaction generated by Waldron et al. [69], who utilised PTFE tubing with Internal Diameters (ID) of 1 mm and 1.59 mm, loaded with 3 and 10 copper spheres of an average diameter of 947 μm , thereby resulting in aspect ratios of 1.06 and 1.68. The inlet concentration of the dichromate solution, c_0 , in the experiments was equal to 0.3884 mM. This value was, also, selected as the inlet concentration for the simulations to enable model validation against the experimental data.

The selection of the number of spheres and channel length was constrained by computational resource limitations. Longer channels would necessitate an increased number of mesh cells, thus increasing the computational effort. It is worth noting that previous CFD simulations, as conducted by Calis et al. [290] and Romkes et al. [294] in the context of pressure drop and mass and heat transfer respectively, demonstrated that even shorter packings, comprising only 8 to 16 particles, adequately represented the flow and mass/heat transfer characteristics of an infinitely long SPSR.

To demonstrate the effect of aspect ratio on the external mass transfer, keeping a constant particle diameter at 947 μm , the diameter of the cylindrical reactor was varied. This resulted in aspect ratios, δ , varying from 1.06 to 1.68, as shown in Table 3-3.

Table 3-3. Reactor I.D, D , aspect ratio, δ , number of spheres, N_{particle} and bed length, L_{reactor} variation for modelled cases of 947 μm spherical particles.

D (mm)	δ (-)	N_{particle} (-)	L_{reactor} (mm)
1.00	1.06	10	9.17
1.14	1.20	10	9.02
1.33	1.40	11	9.34
1.59	1.68	13	9.01

3.3.1. Mesh convergence

Mesh convergence analysis involved an assessment of simulation accuracy with regard to well-established global parameters, including the conservation of flow rate, in terms of average axial velocity, as well as the axial and radial concentration. This evaluation was conducted in a SPSR configuration characterised by a reduced particle count (3 particles) and an aspect ratio, δ , equal to 1.06. The grid-independence study compared three automatically generated meshes produced by COMSOL Multiphysics® v. 6.1, primarily constructed using tetrahedral

cells (Meshes 1-3), with three user-defined meshes based on guidelines from the COMSOL Multiphysics® v. 6.1 manual and technical support, which were built on a background triangular mesh (Meshes 4-6). The primary distinguishing factor among these meshes, apart from variations in background cell refinement, laid in the number of prismatic cell layers at the wall (referred to as boundary elements) to capture boundary layers more accurately. In COMSOL Multiphysics® v. 6.1, this adjustment can be made by modifying the thickness of the initial layer and the number of layers. By default, the initial layer thickness was set at 1/20 of the local domain element height, with the thickness adjustment factor serving as a scaling multiplier for this default size [296]. Further details regarding the specific parameter combinations chosen for each mesh are presented in Table 3-4.

It is important to note that that domain elements define the regions where the physical processes occur and the governing equations are solved numerically, boundary elements represent the interfaces or boundaries between different regions or volumes in the geometry and are used to impose boundary conditions and edge elements represent the edges or boundaries of geometric entities such as surfaces or volumes and are used to partition the model's geometry into finite elements for numerical analysis.

Table 3-4. Investigated physics and user-controlled mesh features in COMSOL Multiphysics® v. 6.1 for a SPSR configuration consisting of 3 particles.

		No of elements
Physics-controlled mesh	1	145340 domain elements, 24128 boundary elements, and 1063 edge elements.
	2	393884 domain elements, 51994 boundary elements, and 1621 edge elements.
	3	1300166 domain elements, 130496 boundary elements, and 2623 edge elements.
User-controlled mesh	4	1225058 domain elements, 83906 boundary elements, and 1467 edge elements.
	5	1827448 domain elements, 115202 boundary elements, and 1962 edge elements.
	6	6614334 domain elements, 222788 boundary elements, and 3000 edge elements.

Based on the number of elements presented in Table 3-4, Mesh 6 exhibited the highest degree of cell refinement in both domain and boundary elements across all examined meshes and was, therefore, chosen as the reference mesh. However, it is important to note that a larger number of elements can increase computational costs, making it essential to find an optimal balance between mesh resolution and computational feasibility. The radial and axial concentrations of the dichromate anions along a line extending the length and diameter of the reactor (coloured in red) were compared across each mesh, as depicted in Figure 3-5a and

Figure 3-5b, respectively. Figure 3-6 presents the velocity magnitude along the same axial line (Figure 3-5a) that is aligned with the primary flow direction (x-axis).

Figure 3-5a and Figure 3-5b underscored the significance of achieving a balanced distribution of domain and boundary elements that ultimately dictated the performance of a mesh in simulations. Notably, Mesh 4, characterised by a high number of domain elements but fewer boundary elements in comparison to meshes with similar number of domain elements (Meshes 3 and 5), exhibited the largest discrepancies in concentration both axially (Figure 3-5a) and radially (Figure 3-5b) when compared to Mesh 6. While the remaining meshes accurately captured the concentration gradient, as indicated by the nearly identical concentration profiles shown in Figure 3-5, only Meshes 3 and 5 showed a deviation of less than 1% in average concentration when compared to Mesh 6. Figure 3-6 provided the answer for the optimal mesh choice, as it illustrated minimal discrepancies between the velocity profiles of Meshes 3 and 6. Heightened velocities were observed in the gaps between the particles and the wall, while zero velocities were noted in the stagnant regions near the contact points with the wall. Consequently, Mesh 3 was deemed the most suitable choice for all subsequent simulations, effectively capturing the critical flow characteristics and concentration gradients.

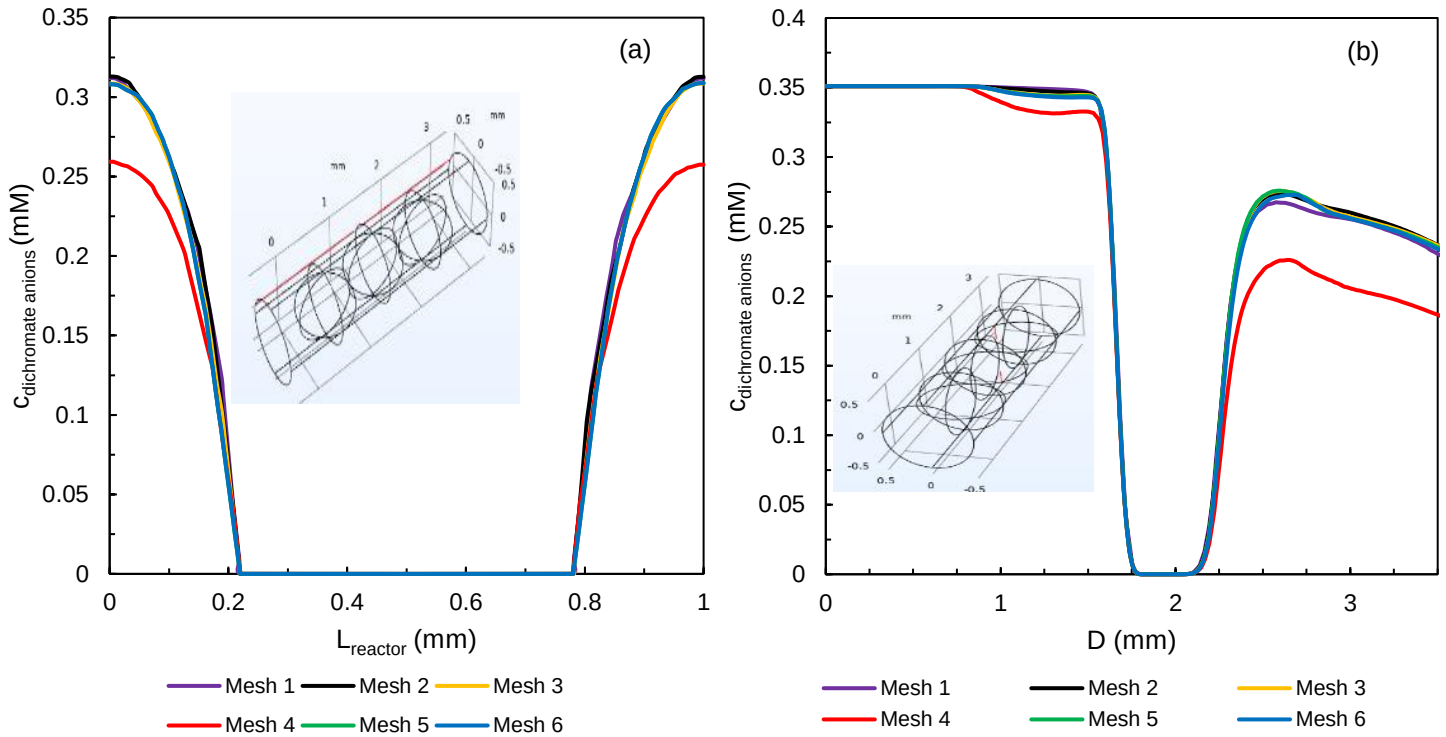


Figure 3-5. Concentration of dichromate anions for different mesh structures along a line extending (a) the length (axial direction) and (b) diameter (radial direction) of the reactor.

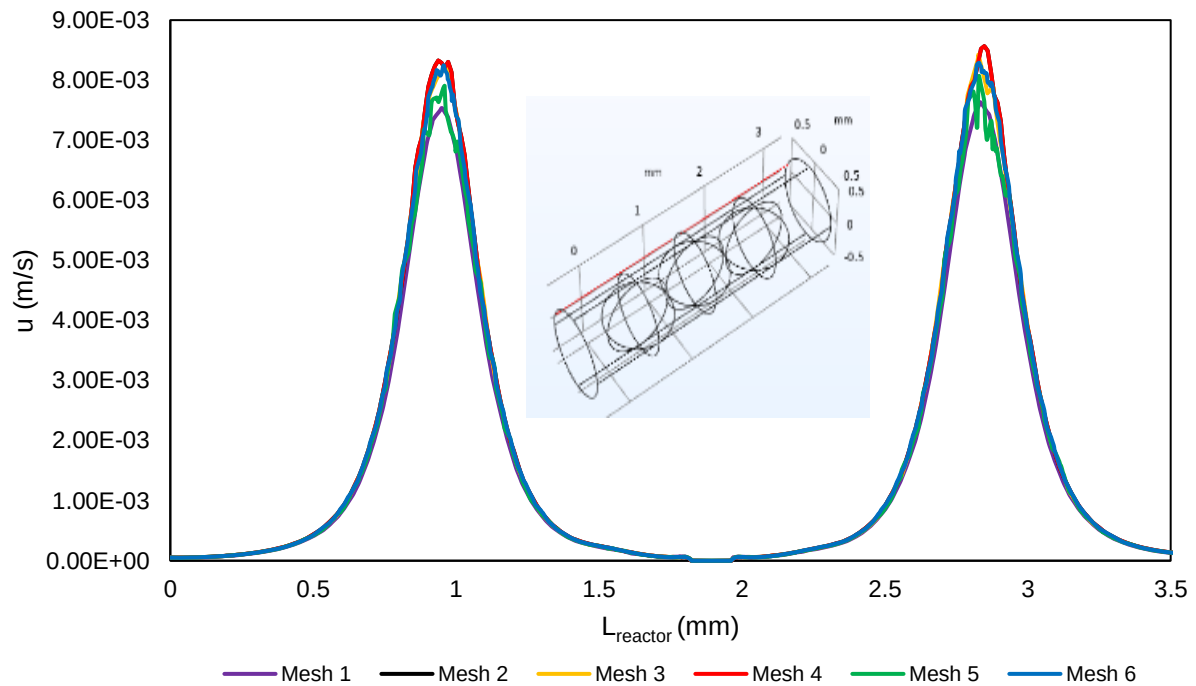


Figure 3-6. Velocity magnitude along a line extending the length (axial direction) of the reactor.

3.3.2. Model validation

To validate the model against the experimental findings of Waldron et al. [69], three SPSR configurations were considered, as illustrated in Figure 3-7a, Figure 3-7b and Figure 3-7c, enabling a comprehensive assessment of the model's predictive capabilities.

- a) The basic design (Figure 3-7a) consisted of a tube with either 1 mm or 1.59 mm I.D. and 3 or 10 copper particles with a diameter of 947 μm (resulting in aspect ratios of 1.06 and 1.68, respectively). It was assumed that the inlet flow was fully developed.
- b) The extended design (referred to as 'extended design 1', Figure 3-7b) closely resembled the reactor used in the experimental setup by Waldron et al. [69]. This configuration included a section of glass beads with a mean diameter of 710 μm positioned upstream of the reactor bed to ensure fully developed flow profile.
- c) Another extended design (denoted as 'extended design 2', Figure 3-7c) featured a short bed of inert fines with diameter equal to 0.2 times the particle diameter ($0.2 \cdot d_p$) and a length equal to the particle diameter, d_p , located upstream of the catalytic bed. This configuration aimed to enforce near-plug flow behaviour, mirroring the reactor simulated by Fernengel et al. [297].

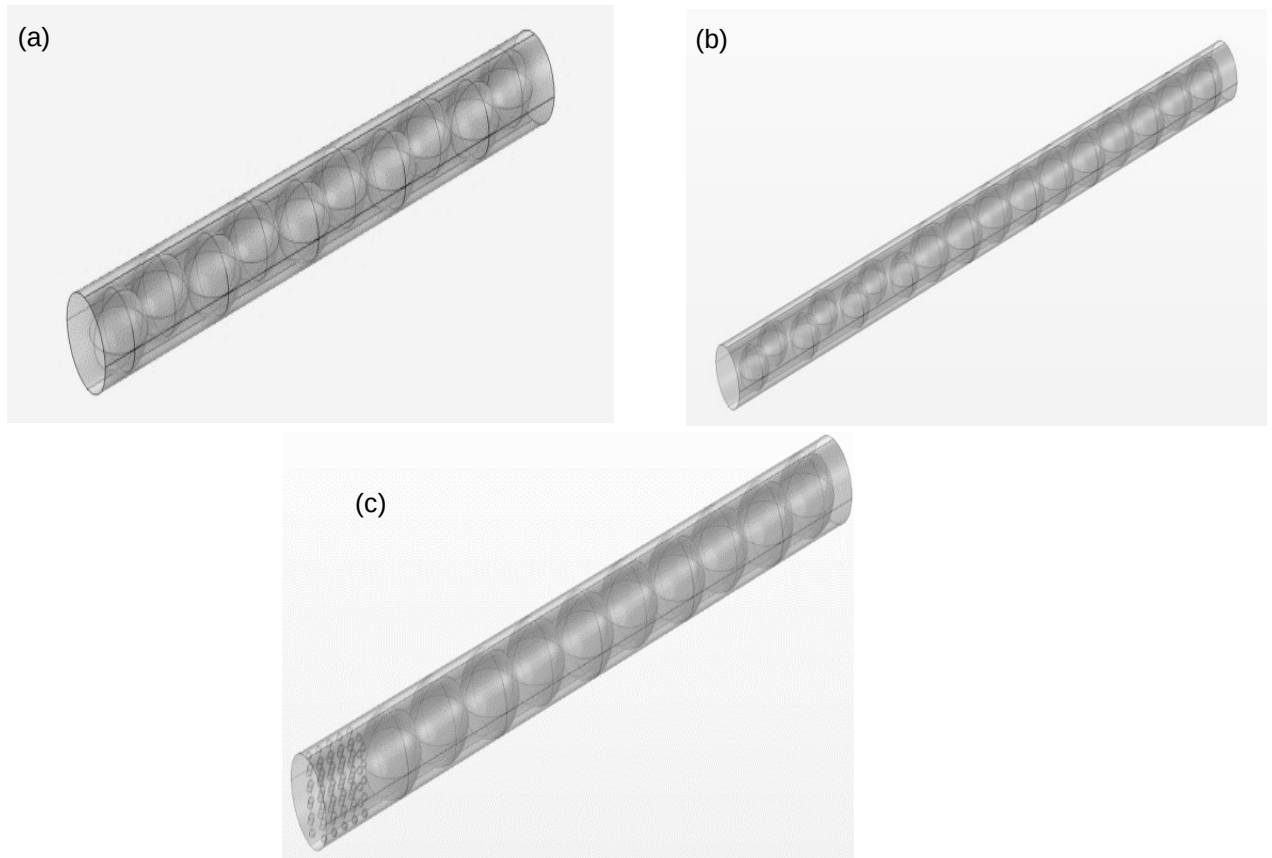


Figure 3-7. SPSR configurations for model validation against the experimental data of Waldron et al. [69]: (a) Basic reactor design (10 pellets, $\delta=1.06$), (b) Extended reactor design with 7 glass beads located upstream of the reactor bed (10 pellets, $\delta=1.06$), (c) Extended reactor design with a short bed of inert fines located before the reactor bed (10 pellets, $\delta=1.06$).

In Figure 3-8, the simulated results in terms of outlet mixed-cup concentration (Equation 3-25) are presented for various configurations across ranges of experimental flowrates. The choice of outlet mixed-cup concentration as the parameter for validation was informed by the experimental concentration data obtained at the reactor outlet by Waldron et al. [69], which were derived using UV-vis spectroscopy. Figure 3-8 demonstrated that, while extended design 1 facilitated a more realistic representation of the flow profile, it was evident that the outlet concentrations among the three configurations exhibited negligible variation for different flowrates (relative error < 2%). Consequently, the basic design, offering a simpler configuration and faster computational time, was chosen.

In Figure 3-9, a comparison between experimental [69] and simulation results for the basic design (Figure 3-7a) is presented for different numbers of catalytic particles and aspect ratios for a range of experimental flowrates. From Figure 3-9, it can be deduced that the agreement between experimental and simulated results for the investigated cases was notable. However, in modelling the SPSR, several assumptions were made, introducing potential errors when comparing experimental and computational data. Deviations from experimental data can be attributed mainly to:

- a) The assumption of uniform copper particle size, while in the experiments by Waldron et al.[69], a range of particle diameters with a mean deviation of $\pm 11 \mu\text{m}$ was used.
- b) The use of constant values of fluid properties (molecular diffusion coefficient, density and viscosity), taken from the literature [291], and considered uniform along the length and diameter of the reactor and independent of temperature.
- c) The packing of the reactor in the simulations approximated the experimental configuration but was not identical.

Considering these factors, despite the introduction of errors, no misleadingly large offset between experimental data and CFD results was observed.

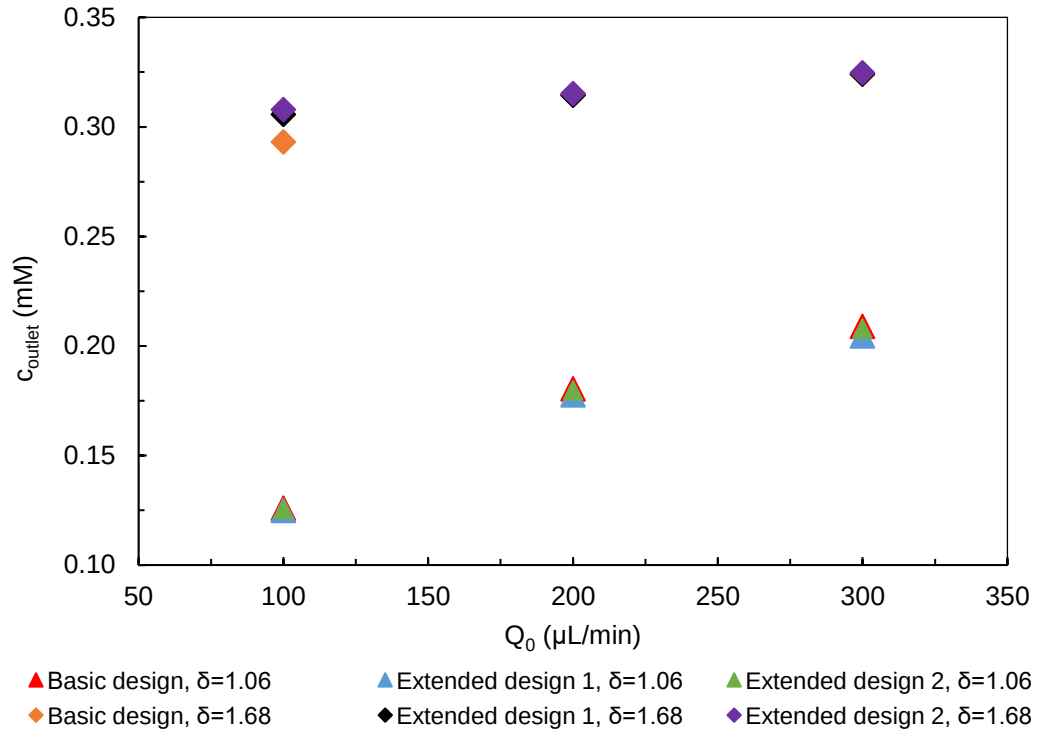


Figure 3-8. Comparison of the outlet mix-cup concentrations for the three simulated reactor configurations for $\delta = 1.06$ and $\delta = 1.68$.

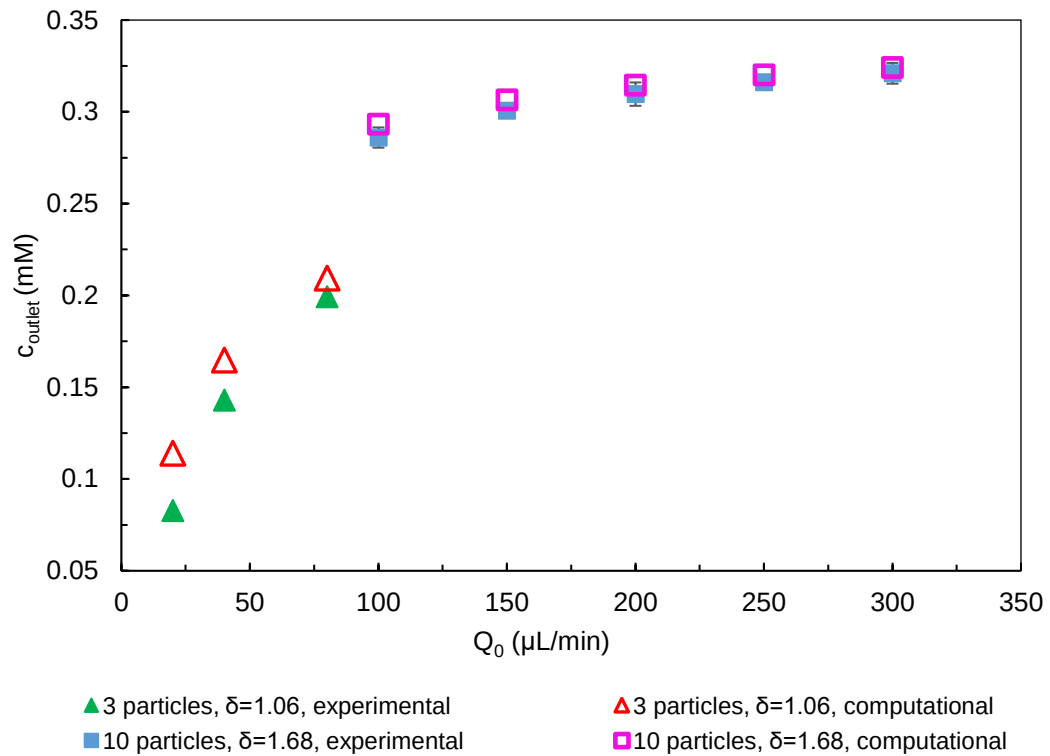


Figure 3-9. Comparison of experimental and CFD mix-cup outlet concentrations for the basic design of a SPSR consisting of 3 and 10 copper particles for $\delta = 1.06$ and $\delta = 1.68$.

3.4. Results and discussion

3.4.1. Flow characteristics

Figure 3-10 presents the packing structures and the flow fields for the CFD simulations at the symmetry xy-plane, passing through the spheres' centre. As validated by Petrazzuoli et al. [284] for all packing structures investigated (the aspect ratio, δ , is smaller than a critical value, δ_c equal to 1.87, where the packing ceases to be deterministic in nature), the particles were arranged in a planar and alternating fashion. This arrangement entailed that each particle (excluding the first and last) touched the wall and two neighbouring particles; one preceding and one following it. Additionally, the flow alternates between each side of the particles, due to the wall confinement.

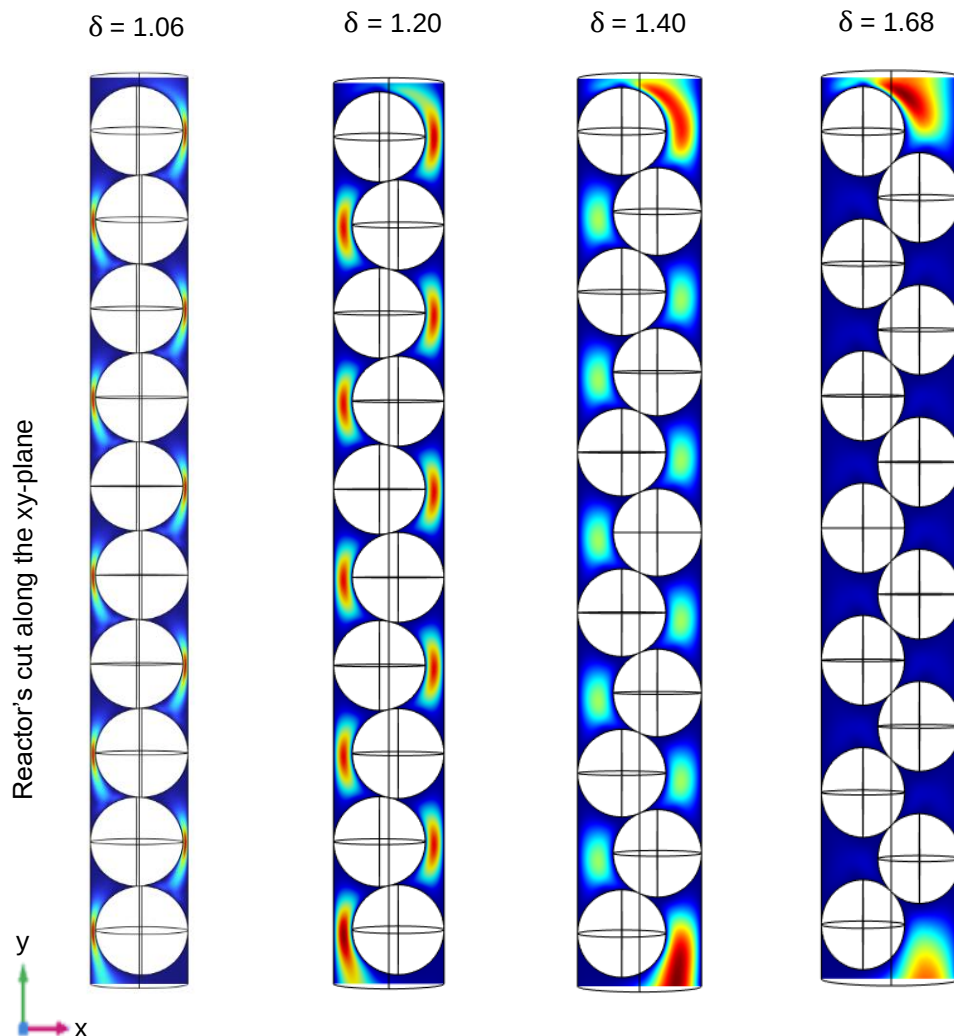


Figure 3-10. Packing structures for chosen values of δ . Particles are in white, and the fluid zone is coloured by velocity magnitude for $Re_h = 20$ (red = fastest flow, dark blue = slowest flow, the scale is different for each case).

Figure 3-11 illustrates the 3-D velocity profile represented by streamlines for both the lowest ($\delta = 1.06$) and highest ($\delta = 1.68$) aspect ratios and $Re_h = 20$. In the configuration with the smallest aspect ratio (Figure 3-11a), where particles were tightly packed inside the reactor and the space between the solids was limited, the flow exhibited pronounced helical characteristics. In more detail, Figure 3-12a presents the velocity magnitude on the xy symmetry plane, extending 4 particles along the axial (x-axis) direction, in the form of velocity vectors for $\delta = 1.06$ and $Re_h = 20$. Based on Figure 3-12a, the flow accelerated in the open spaces near the walls, intricately navigating around particle-particle contact points. Within regions of particle-wall contact, characterised by highly constrained flow, the fluid flow slowed significantly, approaching quasi-stagnation. This observation underscored the existence of stagnant fillets near contact points, where pure diffusion emerged as the primary mechanism governing mass transport, a phenomenon that can be visualised by the orientation of the vectors and the velocity magnitude, as shown in Figure 3-12b. For the highest aspect ratio (Figure 3-11b), with particles still centrally arranged, there was increased vacant space extending from the upper and lower hemispheres of the particles to the reactor walls. Consequently, the velocity of the flow was higher in these areas. Preferring paths of lower resistance, the fluid exhibited reduced interaction with the particles, resulting in channelling, an undesired phenomenon, commonly attributed to the random packing of packed beds [316].

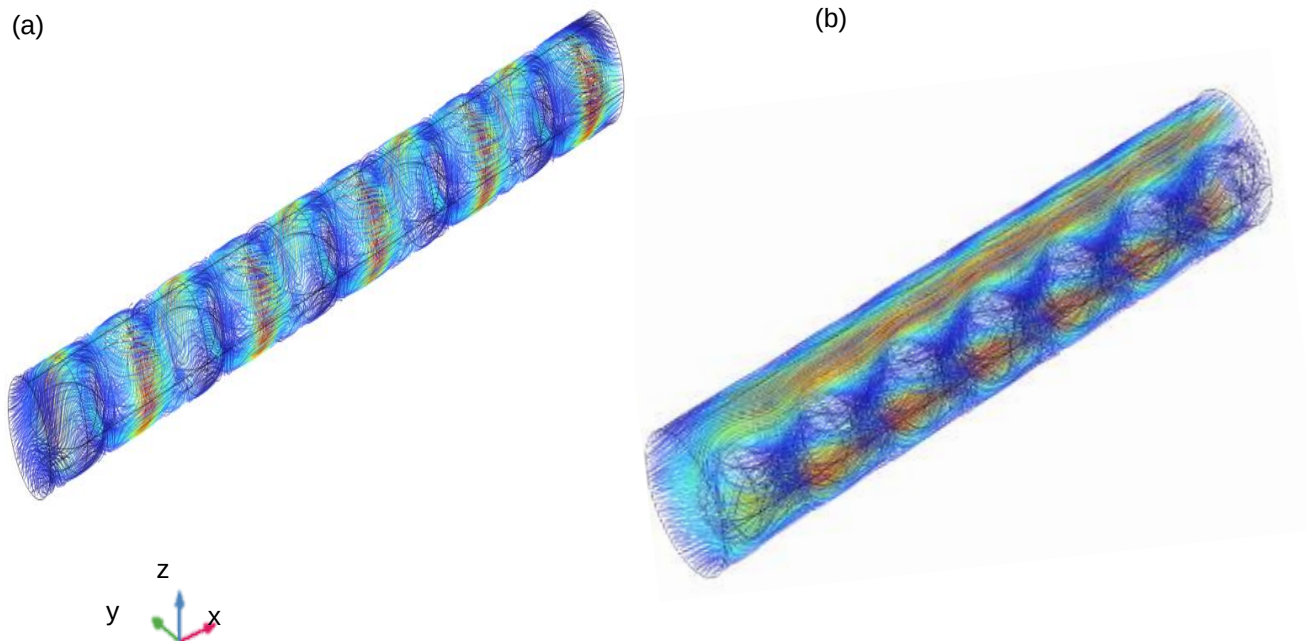


Figure 3-11. 3-D flow profile, delineated by velocity streamlines for a) $\delta = 1.06$ and b) $\delta = 1.68$ at $Re_h = 20$. The streamlines are colour-coded based on the velocity magnitude (red = fastest flow, dark blue = slowest flow).

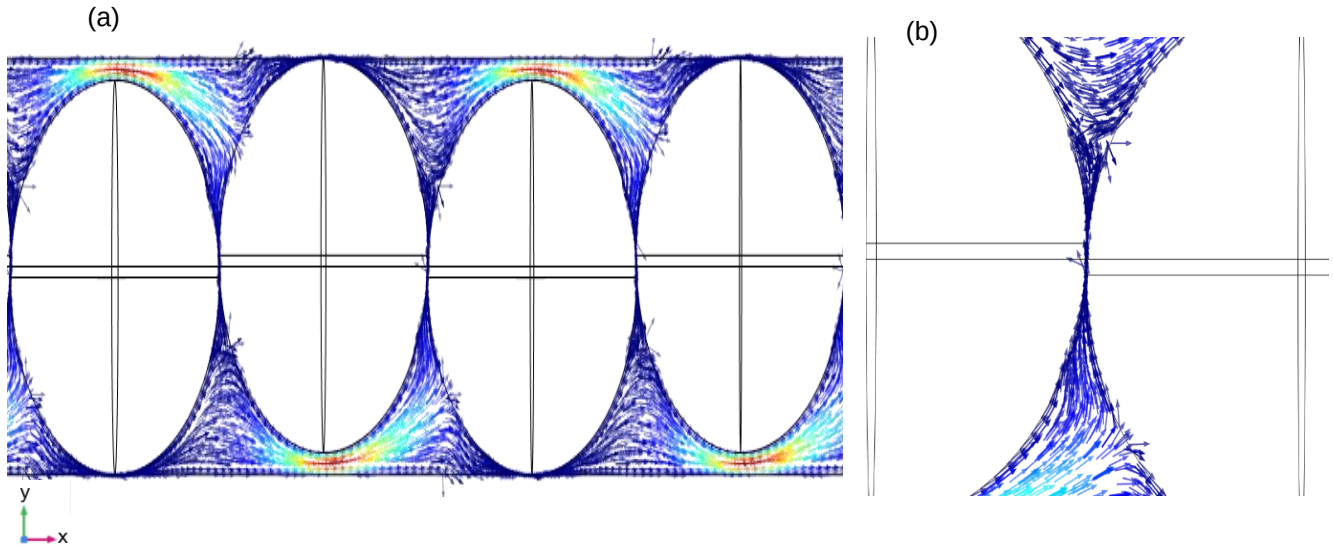


Figure 3-12. Tangential velocity vectors (a) on the symmetry plane $xy=0$ and (b) zoomed-in the contact points of the spheres for $\delta = 1.06$ at $Re_h = 20$. The velocity vectors are coloured according to their magnitudes (red for high velocity and dark blue for low), their length is normalised, and they are placed uniformly on the defined plane.

The phenomenon of fluid bypassing can be effectively elucidated by generating iso-surfaces to depict the concentration distribution of dichromate anions along the bed, as illustrated in Figure 3-13a and Figure 3-13b. It is noteworthy that, in both instances presented, Reynolds number (Re_h) was maintained at 100. In the scenario with a low aspect ratio ($\delta = 1.06$), the bulk concentration exhibited a gradual decline as the fluid traversed over the spheres. Conversely, in the case of a high aspect ratio ($\delta = 1.68$), a substantial proportion of the initial bulk concentration reached the outlet without undergoing significant reaction.

Moreover, owing to the alignment of the particles, a consistently observed symmetrical flow pattern was evident across all cases of aspect ratio, as depicted in the yz -planes of Figure 3-14a and Figure 3-14b for the same inlet flowrate. Notably, the flow exhibited periodicity for all particles downstream from the initial one for aspect ratios of 1.06 and 1.20 and after two particles for aspect ratios of 1.40 and 1.68, thus underlining the importance of maintaining a sufficient number of particles to minimise the impact of inlet effects. Moreover, as shown in Figure 3-14c and Figure 3-14d and in accordance with the observations of Petrazzuoli et al. [284], the cross-sectional area for the flow was decreasing with decreasing aspect ratio, leading to more pronounced velocity around the particle that alternated from one side of the reactor to the other.

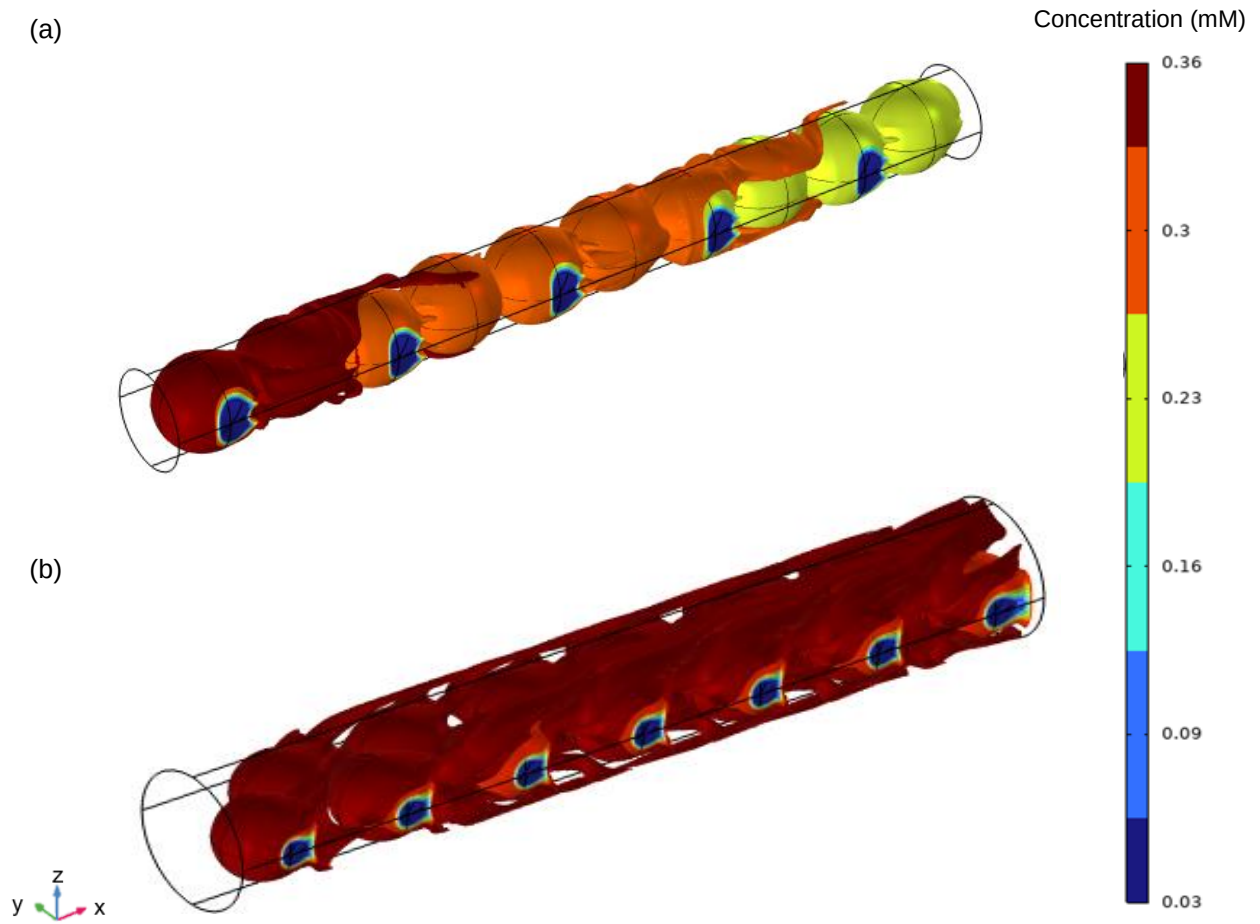


Figure 3-13. 3-D concentration profiles along the SPSR bed in the form of iso-surfaces for (a) $\delta = 1.06$ and (b) $\delta = 1.68$ at $Re_h=100$.

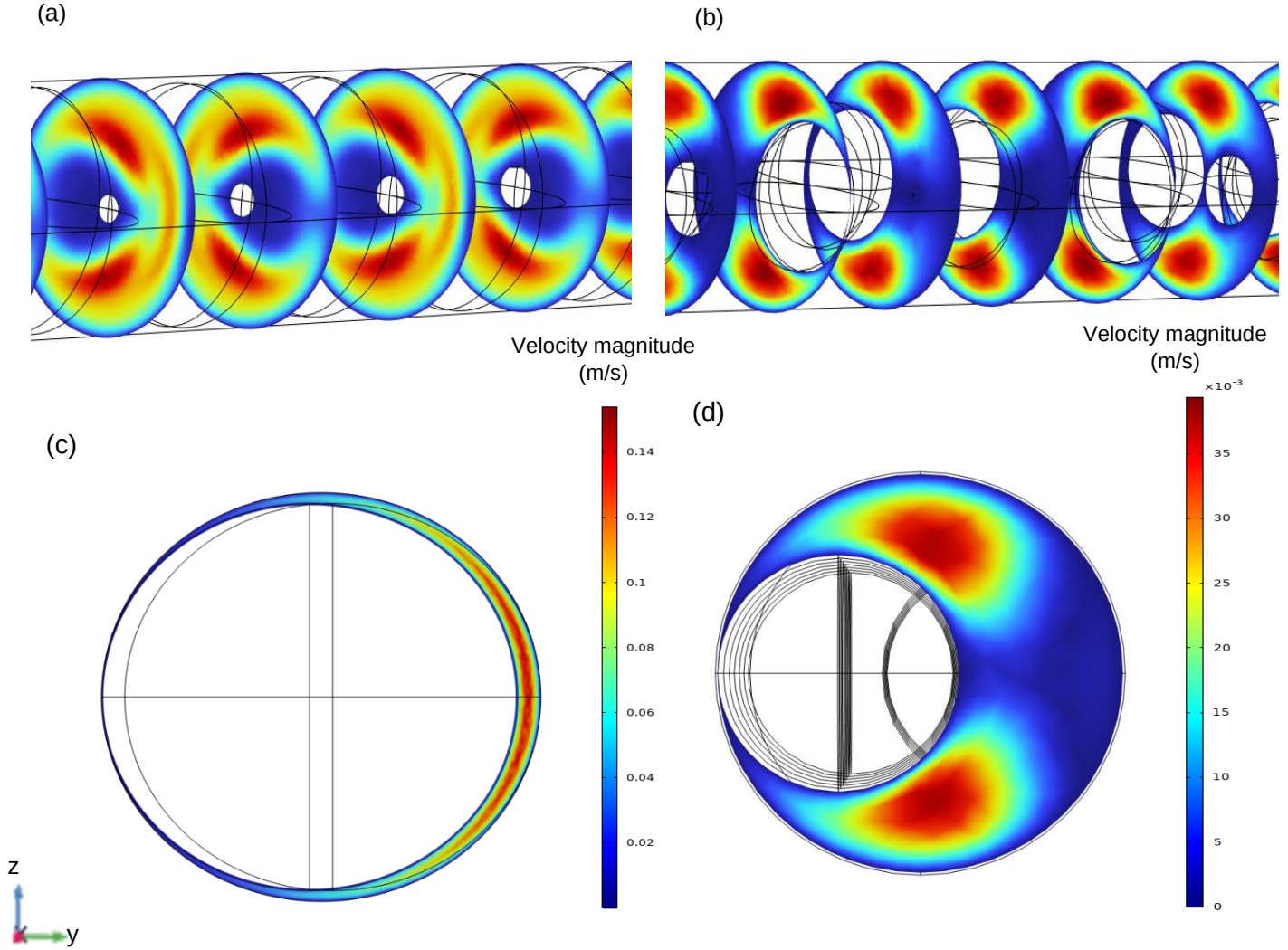


Figure 3-14. Velocity contours on yz planes indicating symmetrical flow patterns for SPSRs of (a) $\delta = 1.06$ and (b) $\delta = 1.68$ and velocity magnitude on a yz plane passing through the centre of a particle for (c) $\delta = 1.06$ and (d) $\delta = 1.68$ for inlet flowrate $Q_0 = 1$ mL/min.

3.4.2. Liquid-to-solid external mass transfer

The simulated external mass transfer was quantified by means of the external mass transfer coefficient, k_{LS} . To facilitate the analysis, the estimated Sherwood numbers (as defined by Equation 3-17) incorporating the external mass transfer coefficient were introduced. In the context of the macroscopic approach, the Sherwood number is represented as Sh_{macro} , while in the microscopic approach, it is denoted as Sh_{micro} .

3.4.2.1. Macroscopic analysis

It has been experimentally [69, 286, 317] and computationally [284, 297] demonstrated that long string reactors behave approximately as plug flow reactors. For the simulations, the length of the packed bed practically equated to the length of the section containing copper particles, $L_{reactor}$, resulting in a length of 1 cm. This configuration was anticipated to deviate

significantly from plug flow. In Figure 3-15, the RTD function, $E(t)$ is presented for the highest ($\delta=1.68$) investigated aspect ratio across different Re_h . Table 3-5 reports the resulting vessel dispersion number, $\frac{D_{ax}}{uL_{reactor}}$, (or inverse Peclet number, Pe^{-1}), commonly employed as criterion to distinguish between models with large deviation from plug flow and those with small deviation from plug flow.

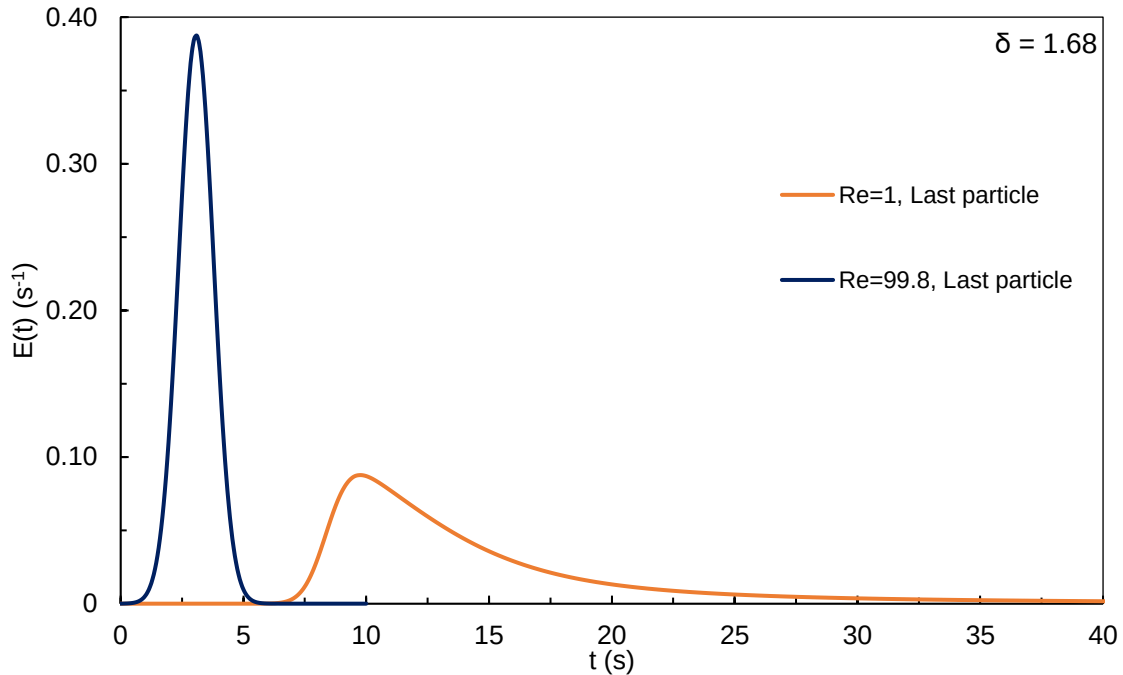


Figure 3-15. Simulated outlet tracer response $E(t)$ curves for open vessel conditions and large deviations from plug flow for SPSRs consisting of 10 particles, with $\delta = 1.68$ and varying Reynolds number, using a diffusive tracer. Re refers to Re_h .

Table 3-5. Vessel dispersion number for the extreme cases of string reactor aspect ratios and studied flowrates.

$Re_h (-)$	$\delta (-)$	$\frac{D_{ax}}{uL_{reactor}} = Pe^{-1} (-)$
2.1	1.06	0.099
1	1.68	0.312
99.2	1.06	0.058
99.8	1.68	0.174

Observing the $E(t)$ curves of Figure 3-15 and reviewing the vessel dispersion numbers presented in Table 3-5, it is evident that all investigated configurations exhibited a high degree of dispersion ($\frac{D_{ax}}{uL_{reactor}} > 0.01$). With increasing deviation from plug flow, the residence time distribution $E(t)$ exhibited a more asymmetric shape. This asymmetric shape with tailing for the case of low Reynolds number can be attributed to the presence of stagnant zones between solids, which retained the tracer longer, indicative of the higher contribution of molecular diffusion towards axial dispersion than the contribution from flow hydrodynamics [318]. These observations are in line with those of Fernengel et al. [297].

The estimated values of the axial dispersion coefficient were compared against the ones proposed by Rastegar and Gu [313], applied for spherical particles in packed beds, as shown in Figure 3-16. Based on Figure 3-16, it can be deduced that for $\delta = 1.06$, the axial dispersion coefficient calculated from the Rastegar and Gu correlation [313] was smaller than the one estimated for $\delta = 1.69$ and increased, as expected, with increasing Reynolds numbers. Small discrepancies were observed when employing the Rastegar and Gu correlation [313] (Equation 3-33) for $\delta = 1.06$, with slight underestimation of the computed axial dispersion coefficients for high Reynolds numbers. In the case of high aspect ratio ($\delta = 1.68$), the highest offset between the calculated values of the two methodologies was observed for $Re_h > 50$. The progressive increase of the passages around the particles that act as bypasses (as explained in Section 3.4.1), led to increased axial dispersion, which was less pronounced in smaller velocities as the molecules had more time to diffuse in and out of these passages. Moreover, the influence of void fraction appears to be stronger in the case of estimated dispersion in SPSRs than in packed beds, as also observed by Petrazzuoli et al. [284]. However, the effect of the axial dispersion coefficients on the estimated mass transfer coefficients for all the range of aspect ratios was on average less than 7% for the investigated Reynolds numbers.

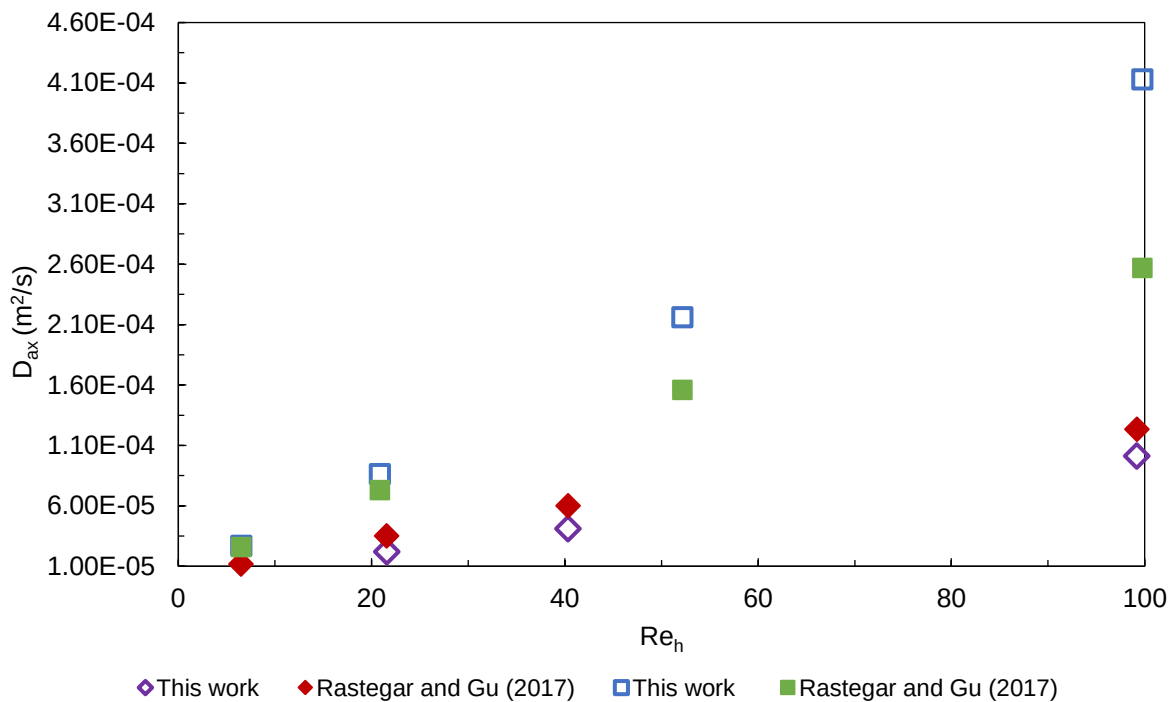


Figure 3-16. Comparison of the estimated axial dispersion coefficient, D_{ax} , based on the RTD curves for SPSRs of this work and the correlation proposed by Rastegar and Gu [313] for packed beds of spherical particles. Different shapes of marks represent the different aspect ratios: $\blacklozenge$: $\delta = 1.06$ and $\blacksquare$: $\delta = 1.68$.

The estimated Sherwood number with (Sh) and without (Sh') consideration of axial dispersion against the hydraulic Reynolds numbers, Re_h , are illustrated in Figure 3-17a, along with the corresponding estimated mass transfer coefficients, $k_{LS}\alpha$ and $k_{LS}\alpha'$, (Figure 3-17b) with increasing superficial liquid velocity, u_0 for all investigated aspect ratios. In all cases, Sh was higher than Sh' , as axial dispersion tends to decrease the driving force available for mass transfer [292]. The effect of axial dispersion observed in this study increased with a decrease in Reynolds number. Sh was approximately 6% higher than Sh' at $Re_h = 5$ and 1% higher than Sh' at $Re_h = 100$. Therefore, the influence of axial dispersion was minimal and can be neglected at higher Reynolds numbers, aligning with the findings of Cao et al. [299], Wakao-Funazkri [305] and Tidona et al. [291]. The enhancement in mass transfer with increased liquid velocity can be attributed to the shrinkage of the effective liquid film corresponding to the diffusion zone surrounding the solid particles. Higher Sherwood numbers were observed for $\delta = 1.06$, with a decreasing trend, as the aspect ratio increased.

The comprehensive comparison between the results of the macroscopic and microscopic models is undertaken in Section 3.4.3, following the presentation of the microscopic model results.

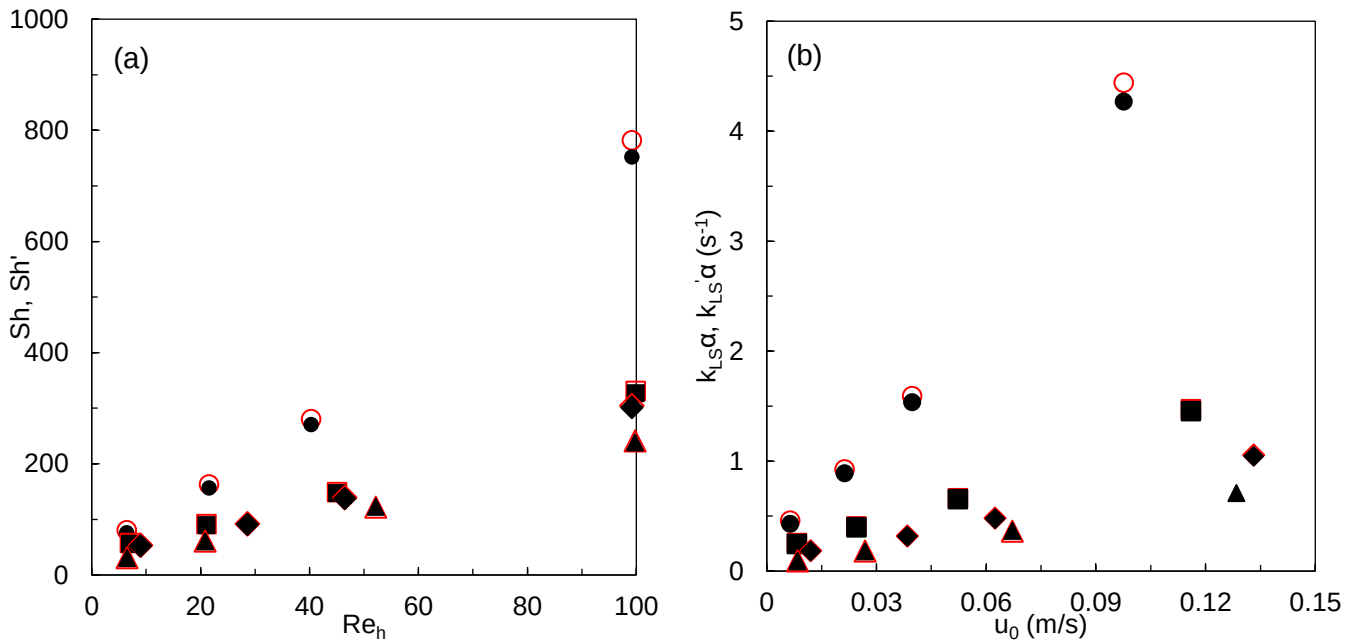


Figure 3-17. (a) Sherwood number versus hydraulic Reynolds number for liquid phase flow with (Sh , open red marks) and without (Sh' , solid black marks) consideration of axial dispersion. (b) Volumetric mass transfer coefficient versus superficial liquid velocity with ($k_{LS}\alpha$, open red marks) and without ($k_{LS}\alpha'$, solid black marks) consideration of axial dispersion. Different shapes of marks represent the different aspect ratios: $\bullet$: $\delta = 1.06$, $\blacksquare$: $\delta = 1.20$, $\blacklozenge$: $\delta = 1.40$, $\blacktriangle$: $\delta = 1.68$.

3.4.2.2. Microscopic analysis

The crux of modelling liquid-to-solid mass transfer within a bed, characterised by a specific channel-to-particle-diameter ratio, hinges on determining the requisite number of particles to

achieve results, akin to infinitely long beds. This necessitated a comprehensive examination, involving a sensitivity analysis on the number of particles employed in the simulation. As elucidated in Section 2.4.1, hydrodynamic periodicity was achieved shortly after the first particle for low aspect ratios and after the first two particles for high aspect ratios.

To ensure that a similar trend arose for mass transport, normal flux on the surface of each particle for an aspect ratio of 1.06 was computed at the lowest Reynolds number investigated ($Re_h = 5$) across three configurations (detailed in section 3.3.2): (a) the basic design featuring 10 copper spheres, (b) an extended design incorporating glass beads upstream the reactor bed and (c) an elongated reactor with 20 copper spheres. Figure 3-18 presents the flux on the external surface of the particles versus the number of particles.

An important observation gleaned from Figure 3-18 was the marginal decrease in molar flux, as a result of the concentration gradient between the bulk fluid and the surface of the particles, for the first two particles, followed by a sharp 25% drop between the second and the third particle, irrespective of the tube hydrodynamic entrance length. An attempt to justify this phenomenon was made by employing the principles of a two-compartment model along the axial direction, approximating mass transfer, for qualitative purposes, as similar behaviour has been reported for monolithic catalytic channels [319] and mass transport in Tube-in-Tube reactors (where a membrane is employed) [320]. Analogous to these cases, in a SPSR two distinct zones were identified: an entrance region (comprising the first two particles for the case of low aspect ratio), where a thin boundary layer around the particles grew and mass transfer resistance was relatively small and a fully-developed region, where the concentration boundary layers around the sphere grew thick enough to merge, leading to a constant mass transfer coefficient.

This observation was further supported by visualising the inlet concentration of dichromate anions spreading along the reactor bed (Figure 3-19a) and the concentration contour on a xy-plane extending through the middle of the reactor height for the first three particles (Figure 3-19b), respectively. The model results were in line with the ones reported by Romkes et al. [294], who proposed that in an 8-particle SPSR of comparable aspect ratio, any particle positioned between the 3rd and 7th, adequately captured heat transfer characteristics, indicating periodicity after the second particle. To mitigate potential back mixing effects at the outlet, which could impact mass transfer in the last particle, the microscopic model, focusing on local fluxes, exclusively considered copper spheres in the fully developed region, excluding the last one. For the sake of efficiency, the calculation of the local mass transfer coefficient was limited to 3-4 particles.

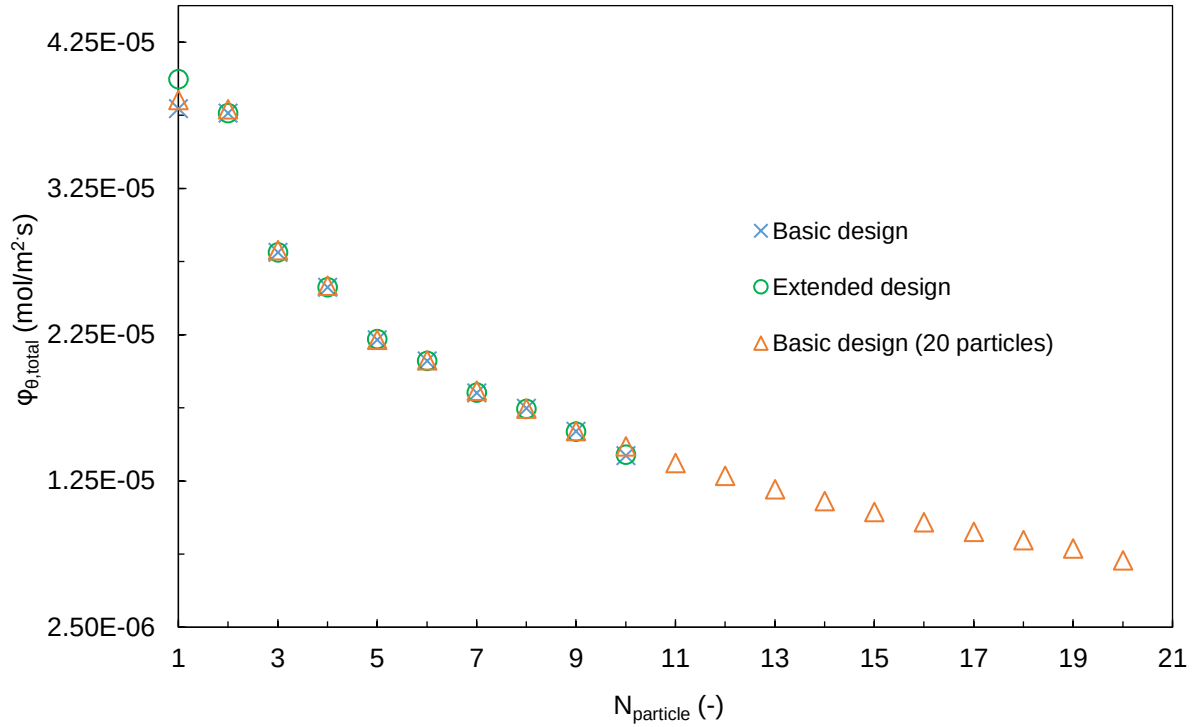


Figure 3-18. Average total normal flux, $\phi_{\theta, \text{total}}$ to the surface of each particle, N_{particle} , in different configurations of a SPSR with $\delta = 1.06$ for $Re_h = 5$.

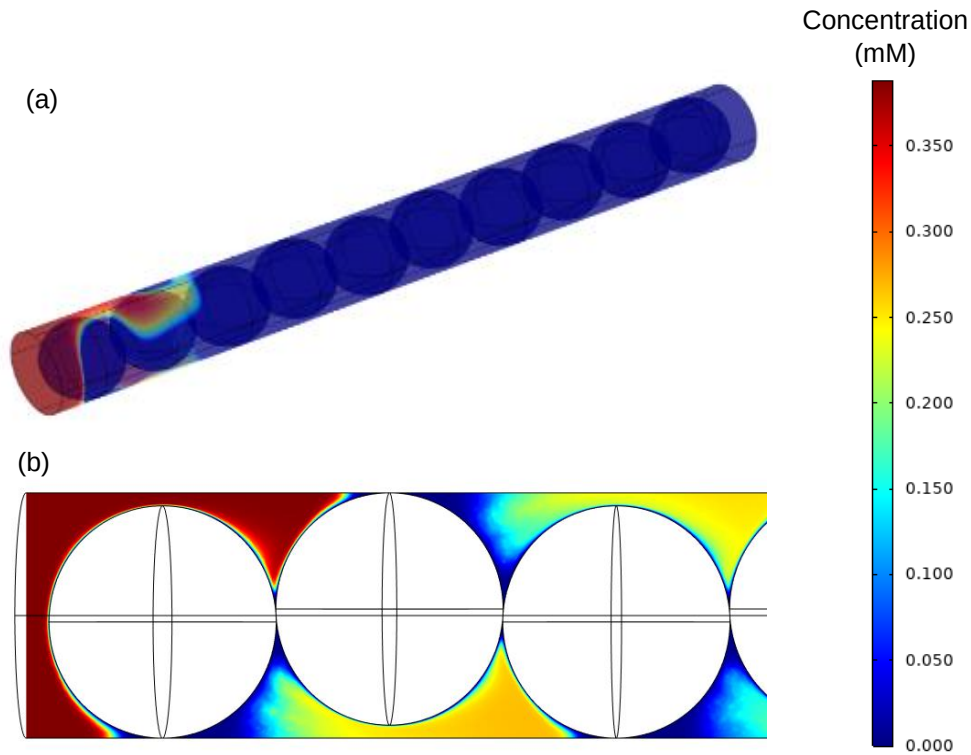


Figure 3-19. (a) 3-D visualisation of the dichromate anions' concentration along the SPSR and (b) 2-D concentration contour of the dichromate anions on a plane extending through the middle of the reactor cross-section for the first three particles for a SPSR with $\delta=1.06$ for $Re_h = 5$.

The diffusion film thickness around the particles was assessed across four Reynolds numbers, Re_h , ranging from a minimum of 5 to a maximum of 100. This evaluation was conducted within 16 crescent sections at different angles, θ around the particle (surfaces of the concentric spheres employed for the post-processing of the results) corresponding to a specific distance from the external particle surface, as explained in Section 3.2.5.2. In each configuration, the point of evaluation within the bulk fluid (distance from the surface of the particles), was determined by considering the available empty space between the sphere and the walls, as well as between consecutive spheres. The concentration profiles around a single particle for a reactor with an aspect ratio of 1.20 for varying Re_h are illustrated in Figure 3-20. Upon examination of Figure 3-20, it is evident that a thin film surrounded the particles, maintaining a thickness of approximately 15 μm for $Re_h < 50$ and slightly below 10 μm for $Re_h > 50$. The film thickness varied with Reynolds number, decreasing as the inlet flowrate (and respective Reynolds number) increased. This behaviour can be attributed to increased convective transport of the solute at higher velocities (partly due to impingement of the flow on the particle surfaces in a SPSR), therefore reducing the thickness of the concentration boundary layer. An analysis of the fluid diffusion zone revealed a linear relationship between concentration at the particle surface and the bulk fluid. Additionally, it can be inferred that the bulk concentration (far from the particle surface) was non-uniform, exhibiting lower values at the points of contact. These variations between crescent sections at different angles diminished with an increase in Reynolds number. Based on these observations, in calculating the local mass transfer coefficient, the concentration at the furthest distance from the particle's surface was used as an approximation of the bulk concentration of the dichromate anions.

In Figure 3-21, the local mass transfer coefficient for each of the 16 crescent sections around the sphere along with the average mass transfer coefficient for each sphere (indicated by dashed lines) is presented across a range of Re_h for reactors with aspect ratios of 1.06 (Figure 3-21a) and 1.68 (Figure 3-21b), respectively. As illustrated in Figure 3-21a and Figure 3-21b, an expected augmentation in the local mass transfer coefficient was observed with increasing Reynolds numbers for both aspect ratios. It is crucial to highlight that, in all instances, the least accurate planes to evaluate the local mass transfer were those near the reactor walls. The proximity to the wall induced a constriction of the boundary layer, posing challenges in accurately assessing the bulk concentration. To facilitate the comprehension of the complex phenomena, each sphere was divided into two hemispheres: the left hemisphere, spanning from 0 to 180°, and the right one, spanning from 180° to 360°. It is also important to note the direction of the flow, going from left to right. Figure 3-21, accompanied by a schematic of the particle arrangement within the reactor, revealed that for both hemispheres, the local mass transfer coefficient tended to be lower at points where spheres were in contact, aligning with

the fluid dynamic observations outlined in Section 3.4.1. In these regions, characterised by relatively stagnant flow, the primary mechanism of mass transfer was diffusion. Furthermore, mass transfer increased and reached local maxima on the surfaces of particles exposed to the open space between spheres and the reactor walls, where fluid was accelerated, followed by a decline indicative of deceleration in fluid velocity. The local mass transfer coefficients of the left hemisphere exhibited higher values than those on the right hemisphere, attributed to the reduced concentration gradient due to the depletion of the bulk concentration. Similar trends were observed for the case of higher aspect ratio, with a shift of the local maxima according to the position of the contact points between successive spheres. Comparing the average values of mass transfer coefficient of Figure 3-21a and Figure 3-21b, for the same range of Reynolds number, it becomes evident that lower aspect ratio resulted in more efficient mass transfer.

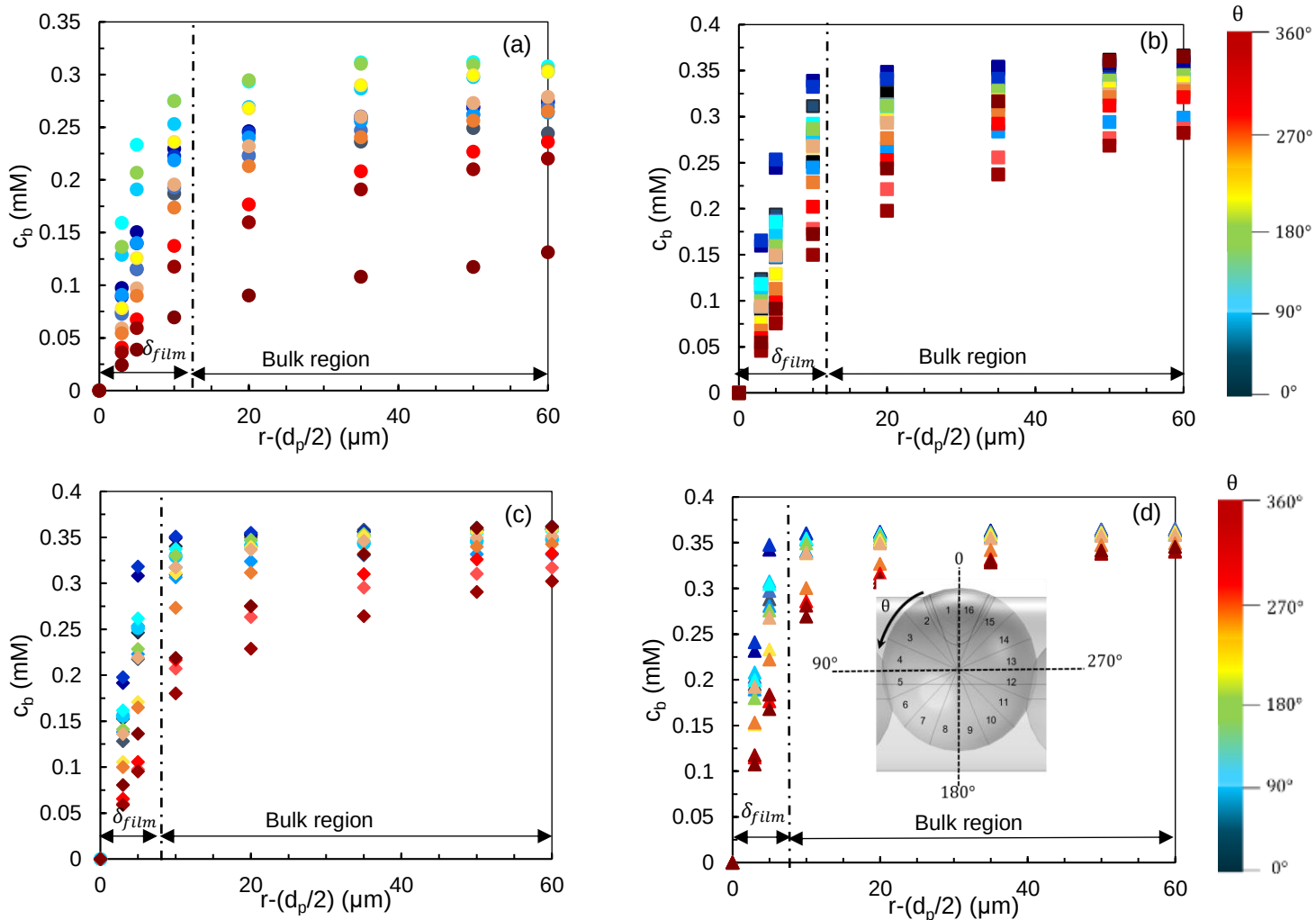


Figure 3-20. Local concentration of dichromate anions around a copper particle, in a SPSR of $\delta = 1.20$, as a function of the distance, r , from its surface, $\frac{d_p}{2}$, for (a) $Re_h = 7$, (b) $Re_h = 21$, (c) $Re_h = 45$ and (d) $Re_h = 100$. The data points are coloured according to the angle of the corresponding crescent section analysed.

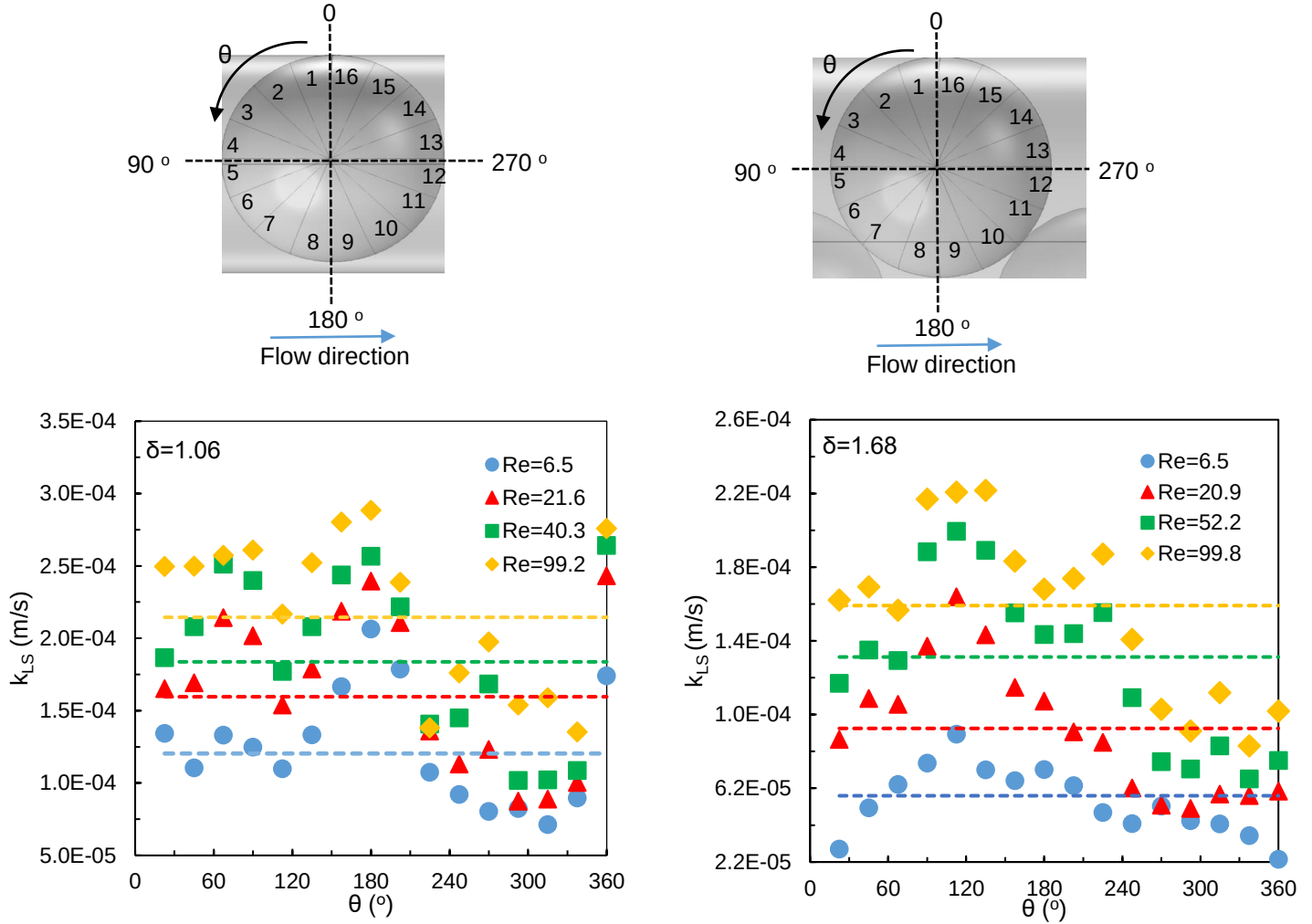


Figure 3-21. Local external mass transfer coefficient vs angle of the corresponding crescent section for different Re_h in SPSR of $\delta = 1.06$ and $\delta = 1.68$. The dashed lines (blue, red, green and yellow) represent the average value of k_{LS} for all 16 sections analysed. Re refers to Re_h .

3.4.2.3. Comparison of the macroscopic and the microscopic approaches

In Figure 3-22, the simulated Sherwood numbers following the macroscopic (Sh_{macro}) and the microscopic approach (Sh_{micro}), respectively, are compared. It can be seen that the highest discrepancy between the microscopic and the macroscopic model was noted for the case of the lowest aspect ratio $\delta = 1.06$, with the difference peaking at $Re_h = 100$, where the Sh_{macro} was 7 times higher than the Sh_{micro} . For aspect ratios bigger than 1.06, the relative difference of the results produced by the two approaches for $Re_h < 50$ averaged 4%. The explanation for these observations lies in the fundamental principles of the two methodologies. In the macroscopic model, mass transfer averaging was performed from the particle scale (micro-scale) to the entire reactor (macro-scale). This involved the assumption that a SPSR containing 10 or 13 spheres served as a macroscale differential volume element with a sufficient number of particles. Each volume element represented a microscale continuum embedded in broader macroscale external fields. This approach holds true for packed beds

or SPSRs with extended lengths, where applying the macroscopic equation to a section of the reactor is representative of the entire system. However, in this work, it was shown that the first 2-3 particles (Figure 3-18) exhibited pronounced mass transfer, which affected the calculated concentration at the outlet, and could potentially lead to an overestimation of the external liquid-to-solid mass transfer coefficient. Moreover, the impact of wall effects, significantly reducing the homogeneity of momentum and mass transfer in both axial and radial directions, was more pronounced for low aspect ratios ($\delta = 1.06$) compared to high aspect ratios ($\delta = 1.68$). The proximity of a wall can create boundary layers, where the flow properties (velocity, concentration) experience significant changes. These boundary layers can lead to non-uniformity in both momentum and mass transfer near the walls. Therefore, as the aspect ratio increases (although δ was less than 10, a typical criterion for negligible wall effects in packed beds), the flow around the particle became less dependent on the aspect ratio and more reliant on the porosity of the reactor. Finally, it is crucial to note that, in the macroscopic model, average values of porosity (ϵ) and surface-to-volume ratio (α) were used for the calculation of the mass transfer coefficient, a choice that could potentially amplify errors. Considering these factors, results from the microscopic approach were deemed more reliable in explaining laminar flow and mass transfer for the SPSR, emphasizing the need for the development of an up-scaling approach [321]. Such an approach should utilise a volume averaging procedure to derive macroscopic equations, incorporating additional contributions to account for small-scale effects on the macroscopic velocity and concentration field.

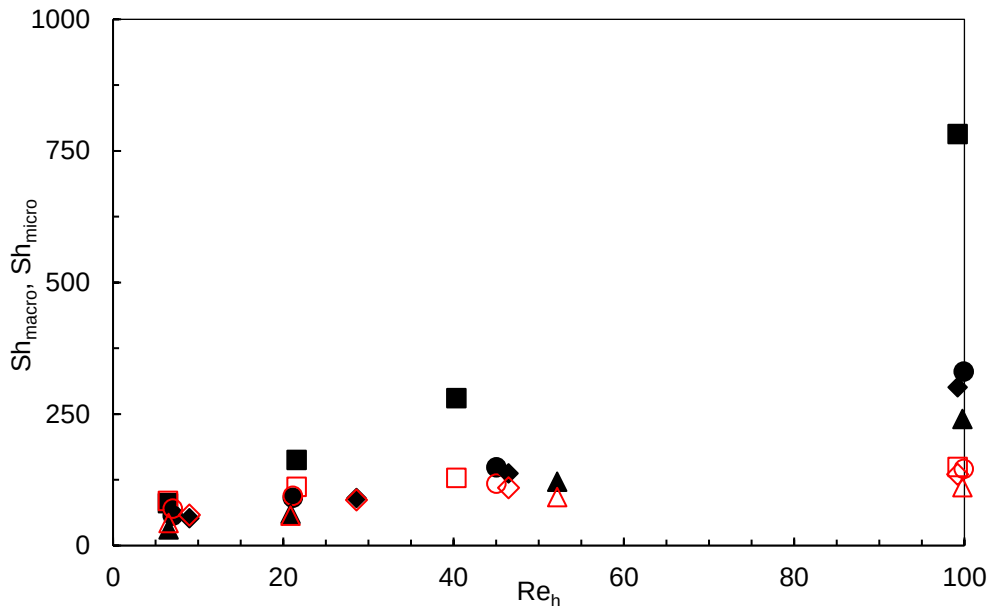


Figure 3-22. Comparison of estimated Sh_{macro} and Sh_{micro} against Re_h for different aspect ratios. Solid black marks refer to the results obtained from the macroscale analysis, whereas open red marks denote the ones from the microscale analysis. Different shapes of marks represent the different aspect ratios: ■: $\delta = 1.06$, ●: $\delta = 1.20$, ◆: $\delta = 1.40$, ▲: $\delta = 1.68$.

3.4.3. External mass transfer coefficient correlations

The simulated microscopic Sherwood numbers were fitted to the commonly used engineering correlation $Sh = 2 + c_1 Re_h^{c_2} Sc^{\frac{1}{3}}$. Four correlations were developed, each specific to a channel-to-particle-diameter ratio, as illustrated in Figure 3-23. Additionally, two generic correlations that are a function of aspect ratio for cylindrical channels with $1.06 \leq \delta \leq 1.68$, with varying levels of complexity and fitting qualities were developed that are listed in Table 3-6. In Figure 3-24, the parity plot for the calculated Sherwood numbers, based on the different correlations proposed in this work, is presented. Figure 3-24 reveals that, regardless of the correlation used, the majority of the calculated Sherwood numbers for both the lowest ($\delta = 1.06$) and the highest ($\delta = 1.68$) aspect ratio fell within an error window of $\pm 20\%$.

Table 3-6. Extracted correlations, fitted constants and their relevant fitting quality, based on CFD simulations.

$Sh = 2 + c_1 Re_h^{c_2} Sc^{\frac{1}{3}}$						(3-37)
Aspect ratio, δ	c_1		c_2		Fitting quality, R^2	
	5.987		0.227		0.997	
	4.101		0.299		0.999	
	3.062		0.351		0.992	
	2.101		0.388		0.990	
≤ 1.68	$Sh = 2 + c_1 \delta^{c_2} Re_h^{c_3} Sc^{\frac{1}{3}}$				(3-38)	
	c_1	c_2		c_3		
	5.229	-0.912		0.283	0.953	
≤ 1.68	$Sh = 2 + c_1 \delta^{c_2} Re_h^{(c_3 \delta^2 + c_4 \delta + c_5)} Sc^{\frac{1}{3}}$				(3-39)	
	c_1	c_2	c_3	c_4	c_5	
	5.802	-1.929	-0.226	0.822	-0.358	0.974

Based on Figure 3-23, Sh values increased with Reynolds numbers and were inversely proportional to the increase in aspect ratio, consistent with the flow patterns reported in Section 3.4.1, where minimal bypassing was observed for SPSR of small aspect ratios. To facilitate a meaningful comparison between the results derived from proposed correlations and the existing literature, it is imperative to employ a standardised definition of the Reynolds number, ensuring consistency across different studies. This entails employing a common Reynolds number definition. In Figure 3-25, the proposed correlations are juxtaposed with the correlation presented by Romkes et al. [294], which is specifically tailored for SPSRs with $\delta \leq 2$, without factoring in the aspect ratio, and defining the Reynolds number based on the hydraulic diameter, d_h . The comparative analysis of Figure 3-25 revealed that the proposed

correlations generally align within the same range as the one delineated by Romkes et al. [294], suggesting an improvement in the liquid-to-solid mass transfer in circular cross section reactors, particularly for $Re_h < 40$ for both $\delta = 1.06$ and $\delta = 1.68$, compared to reactors with square ducts, where dead zones and preferential passages occurred due to geometry. Since the Sherwood number in this work was calculated using the liquid-to-solid mass transfer coefficient, k_{LS} , obtained from the microscopic model, it was feasible to correlate it with Re_0 , without explicitly deriving correlations for it. In Figure 3-26, the values of the calculated Sh against Re_0 are shown for various studies on SPSRs and packed beds with average porosities similar to those studied in this work. Whilst Templis and Papayannakos [288] conducted a similar study, it is important to note that the liquid superficial velocities they employed are 10 times lower than those investigated in this work. Therefore, extrapolating the proposed correlation to higher velocities would lack validation. For the SPSR with the smaller aspect ratio ($\delta = 1.06$), the estimated mass transfer coefficient, in terms of Sherwood number, was higher than the ones calculated by other correlations for SPSRs and packed beds, indicative that the correlations available in the literature for packed bed reactors may not be directly applicable to string reactors with very low aspect ratios. Conversely, for SPSRs characterised by a higher aspect ratio ($\delta = 1.68$), the trends indicate a convergence towards behaviour reminiscent of packed bed reactors.

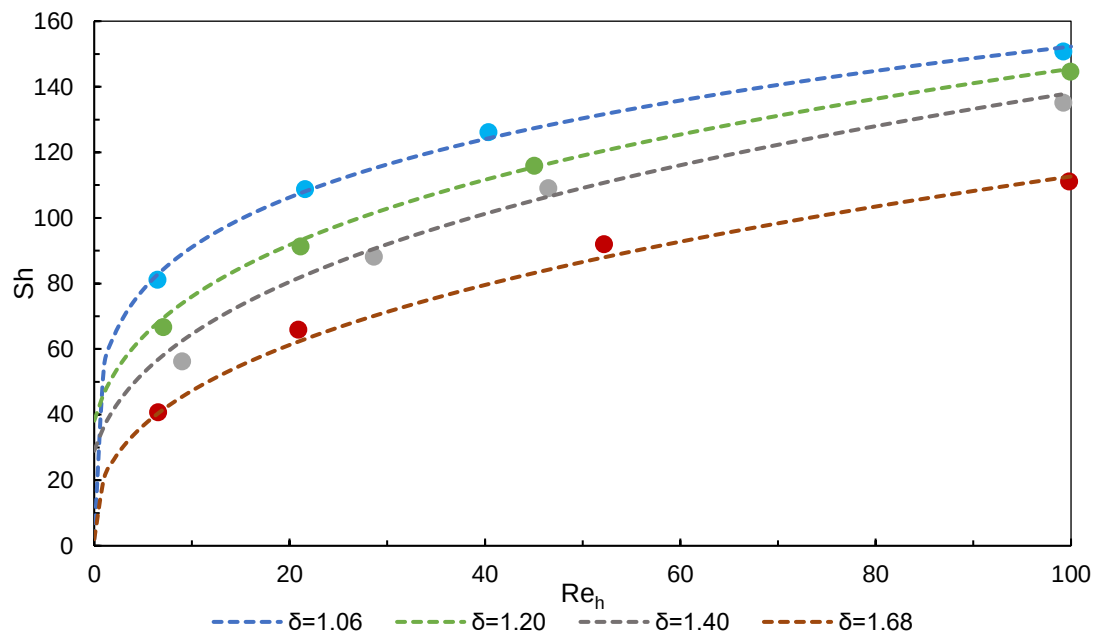


Figure 3-23. Estimated Sh vs Re_h for the examined aspect ratios and the relevant extracted correlations.

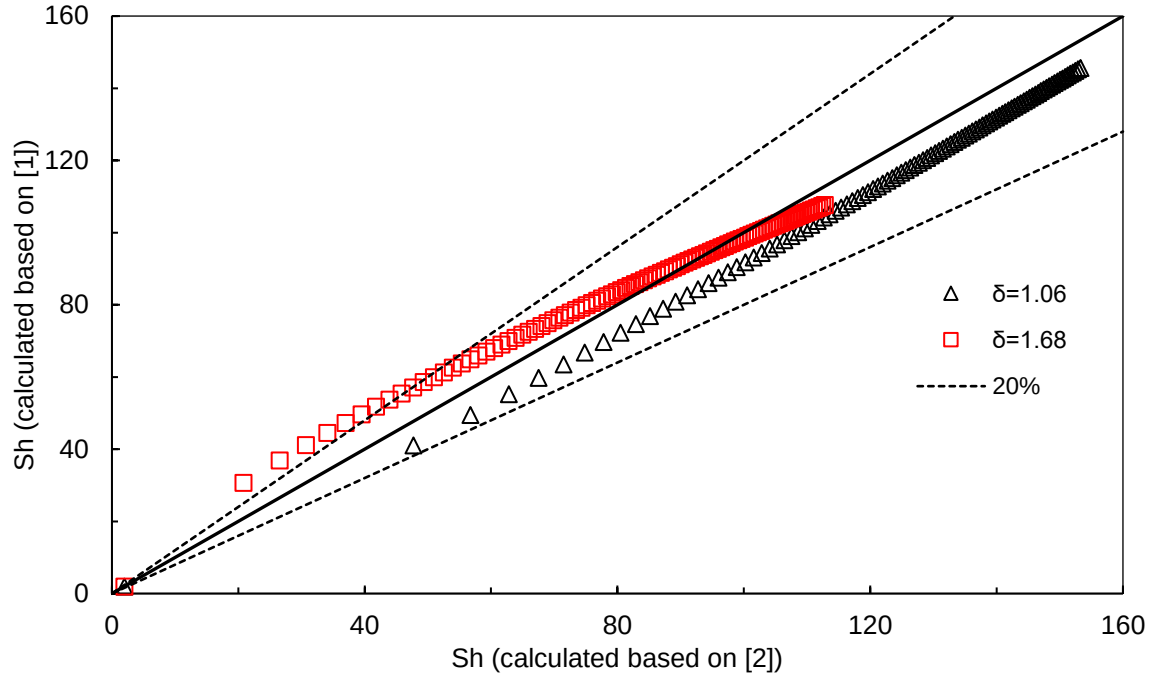


Figure 3-24. Parity plot for the estimated Sh based on the correlations of different fitting quality and level of complexity, proposed in Table 3-6 for SPSR with $\delta=1.06$ and $\delta=1.68$, [1]: $Sh = 2 + 5.229\delta^{-0.912}Re^{0.283}Sc_3^{\frac{1}{3}}$ and [2]: $Sh = 2 + 5.802\delta^{-1.929}Re^{(-0.226\delta^2+0.822\delta-0.358)}Sc_3^{\frac{1}{3}}$.

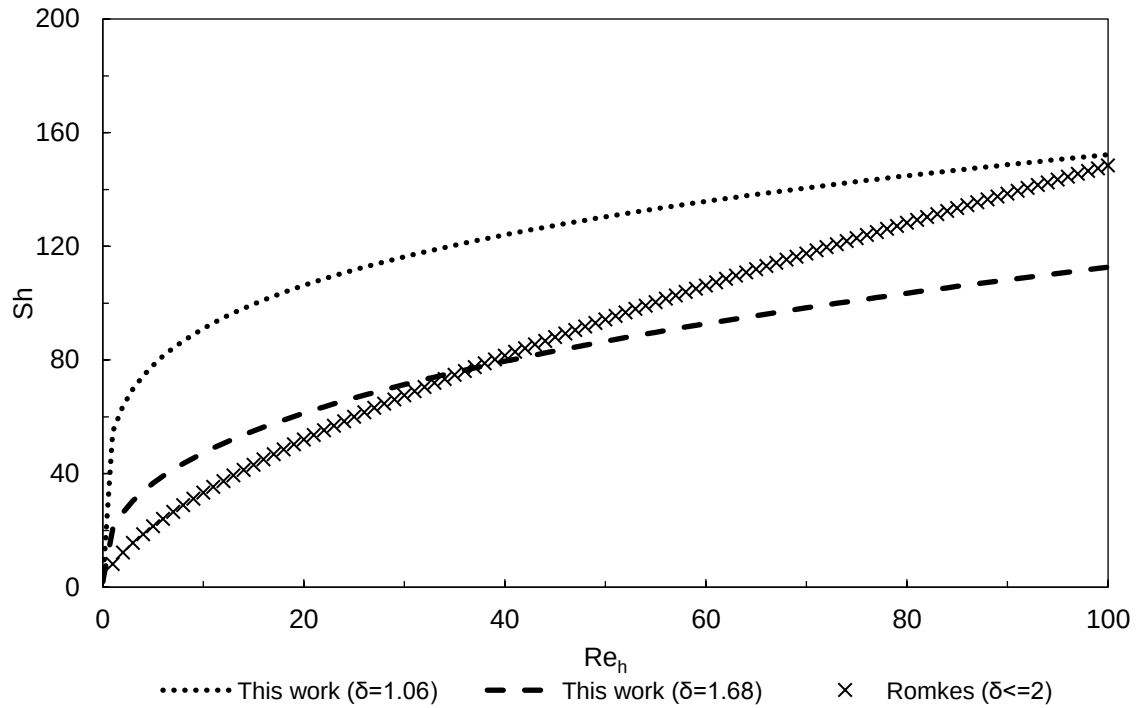


Figure 3-25. Comparison of the calculated Sh vs Re_h based on the correlation proposed by Romkes et al. [294] with the ones proposed in this work for SPSR with $\delta=1.06$ and $\delta=1.68$.

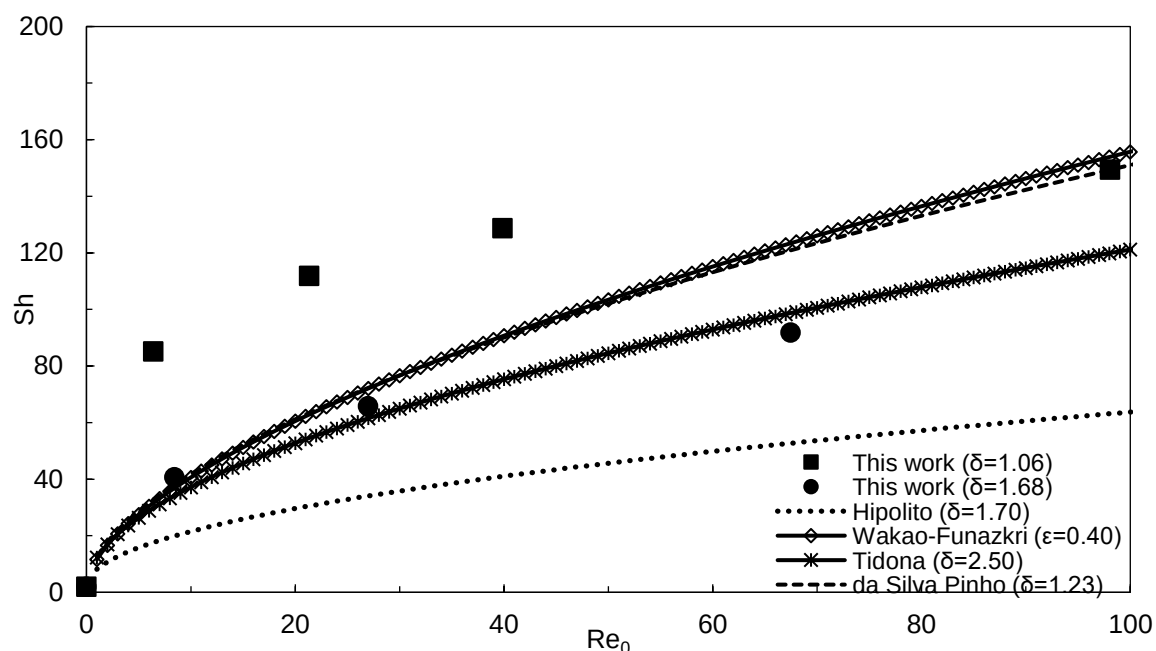


Figure 3-26. Comparison of existing correlations for packed beds and SPSRs with the ones proposed in this work for SPSR with $\delta = 1.06$ and $\delta = 1.68$.

3.5. Conclusions

Flow patterns and liquid-to-particle-mass transfer in a SPSR filled with non-porous spherical particles were studied for aspect ratios varying between 1.06 and 1.68. A model was developed, validated based on experimental data in COMSOL Multiphysics® 6.1, and extended for Re_h values up to 100. The main qualitative features of the flow were presented, and the external mass transfer coefficient was estimated through two approaches: a macroscopic approach, commonly applied to packed beds, involving RTD studies, and a microscopic approach based on the local mass flux calculation and averaging around the spheres. Upon comparing the two methodologies, it became evident that the macroscopic treatment of composite reactors of small aspect ratios, characterised by non-uniformity in both momentum and mass transfer due to pronounced wall confinement, exhibited a significant weakness, leading to an overestimation of mass transfer. For this reason, new correlations were developed based on the microscopic approach, to estimate the liquid-to-solid mass transfer coefficient, elucidating the interplay between hydrodynamics, mass transfer and fast reaction kinetics in SPSRs. These correlations captured the influence of aspect ratio on enhancing liquid-to-solid mass transfer, hence confirming the potential of this reactor concept to be employed for the acquisition of intrinsic kinetics, free of external mass transfer limitations. Finally, two global correlations were formulated—one simplified and one more rigorous—both accounting for the impact of aspect ratio. The correlations developed can be directly employed for the estimation of the external mass transfer coefficient in cylindrical reactors filled with

spherical beads, considering aspect ratios up to 1.68 in the laminar flow region, rendering them a valuable alternative to typically laborious experimental procedures.

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Chapter 4. Esterification of levulinic acid to ethyl levulinate over Amberlyst-15 in flow: Systematic kinetic model discrimination and parameter estimation

4.1. Introduction

Increasing environmental concerns drive the market towards a shift to alternative renewable or sustainable sources as raw materials for fuel and chemical production. Lignocellulosic biomass offers sustainability and economic benefits, without disrupting the food chain and can be converted into valuable bio-based building blocks [322]. Levulinic acid (LA) is a versatile platform chemical that can be produced through acid hydrolysis of renewable biomass, such as wheat straw [323] and sugar cane [324]. The possession of a ketone carbonyl group and an acidic carboxyl group imparts LA the ability to react with different functional groups to form a wide range of derivatives [325, 326]. Alkyl levulinates, produced from the esterification of LA with alcohols, have built up great momentum as fuel additives in gasoline and biodiesel [327] and are expected to witness a rapid growth in the levulinic acid market share by 2030 [328]. Among them, ethyl levulinate (EL) exhibits good compatibility with most gasoline blends [329-331] and has been tested in regular diesel engines to improve combustion [332]. Its sulfur-free nature and degradation via OH radicals [333] contribute to cleaner burning [334], hence paving the way towards emission reductions in the transportation network.

Despite the growing interest in ethyl levulinate, most of the publications on its heterogeneously catalysed synthesis deal with catalyst screening and reusability, with focus on pore geometry and acidity [335-341]. Few kinetic studies of the esterification of levulinic acid to ethyl levulinate have been published in the presence of heterogeneous catalysts [335, 342-345], with only two conducted in a continuous system [345, 346], and without accounting for the interactions between the catalytic sites and the reaction mixture, described by adsorption and desorption phenomena of the participating species. It becomes, thus, clear that there is a gap in the literature regarding a consensus on the reaction mechanism of the esterification of levulinic acid to ethyl levulinate, and the identification of reaction kinetic models that do not constitute solely empirical expressions.

Although the use of batch reactors as a tool for kinetic studies has been well established [347], continuous flow micro-reactors have risen as an attractive alternative in synthesis and reaction optimisation [15, 348]. The higher heat and mass transfer rates in micro-reactor systems enhance the likelihood that intrinsic reaction information is obtained that can aid process scale-up [65]. Moreover, the ease of automation of microfluidic systems allows precise control and tuning of the reaction conditions, with minimal user intervention and maximum consumption efficiency [349], whilst their coupling with inline [50, 67, 176] and online [54, 69, 70] analysis tools enables the expansion of the experimental design space.

Automated flow systems for obtaining reaction kinetics have been successfully applied for homogeneous [10, 29, 65, 265, 350-354] and heterogeneous (where the catalyst is solid) liquid phase [69, 355], gas phase [70] and gas-liquid phase reactions [356]. The first step to obtain a kinetic model involves identifying an appropriate kinetic model structure through screening a number of potential rate laws. Identification is not a trivial task in the case of heterogeneous reactions, as there is a large number of potential mechanistic models with similar structures (e.g., Langmuir-Hinshelwood-Hougen-Watson, Eley-Rideal). The identification of the final rate expression is often based on assumptions that might be difficult to verify on the macroscopic scale leading to similar behaviour in the design space investigated and, therefore, poor distinguishability and necessitating the use of microscale simulation tools [357]. In-situ spectroscopic techniques, such as Raman [48, 358], NMR [359], and FTIR [27, 360-362] can be used to probe the solid-liquid interface in the microscale, however this can be very challenging, in the presence of bulk species and solvents with overlapping signals [363]. The second step after deciding on the suitable model structure is to estimate with statistical satisfaction the kinetic parameters [364], which can often be highly correlated or practically unidentifiable in the chosen experimental design space [365].

The aim of this work is to systematically screen an extensive library of models to obtain the kinetics of the continuous heterogeneously catalysed esterification reaction of LA with ethanol (EtOH), starting from simple reaction rate expressions and building on mechanistic models that are mathematically described by equations containing a high number of kinetic parameters. Amberlyst-15 was chosen as the solid catalyst as it is a low-cost commercially available sulfonic ion-exchange resin [366] with the highest activity among both zeolites and non-zeolitic materials for the esterification of LA [335].

Based on the hydrodynamic study and mass transfer liquid-to-solid correlations developed in Chapter 3, which highlighted the potential of SPSRs for identifying kinetics of heterogeneously catalysed reactions that are not masked by external mass transfer limitations, a Single Pellet String Reactor (SPSR), with spherical Amberlyst-15 particles, packed in a tube of slightly larger diameter, was employed. Considering that increasing the complexity (i.e., number of parameters) of the model structure increases the likelihood of unidentifiable parameters in the experimental design space, an automated platform with online analysis and advanced algorithms for model identification, selection and parameter estimation was developed. Different experimental data sets (with and without product addition) were compared to investigate the impact of the different experimental design variables on kinetic model identifiability. The temperature dependency on the adsorption of the different species was also incorporated in the proposed model structures.

4.2. Experimental procedure

4.2.1. Single Pellet String Reactor

4.2.1.1. Catalyst properties

Amberlyst-15 is a strongly acidic macroreticular polymeric cation exchange resin based upon a crosslinked styrene-divinylbenzene copolymer system, characterised by a complicated pore structure characterised by both gel and non-gel porosity [367, 368]. Boasting a high proton exchange capacity (4.7 meq/g), a surface area of 42 m²/g and structural durability [367, 369], Amberlyst-15 is a highly efficient heterogeneous catalyst in many acid-catalysed reactions, including transesterification, Friedel-Crafts alkylation, halogenation, hydroalkylation [370]. Additional advantages of it include its affordability, non-toxicity, ease of handling, safety in use, and reusability [371]. Previous studies have demonstrated Amberlyst-15 to be the most active among both zeolites and non-zeolitic materials for the esterification of ethyl levulinate, presenting a levulinic acid conversion of 54% [335].

Therefore, Amberlyst-15 (Sigma Aldrich) was chosen as the solid catalyst for the synthesis of ethyl levulinate. The catalyst was dried overnight at 80 °C, sieved, and loaded inside the reactor using a vacuum pump (Edwards Vacuum).

4.2.1.2. Reactor configuration

The reaction was carried out in a Single Pellet String Reactor (SPSR) that consisted of a horizontally coiled PTFE tube (VWR International) with 1 mm inner diameter (I.D.) filled with 0.1 g of Amberlyst-15 spheres (710-850 µm sieve fraction) that composed a reactor bed of approximately 35 cm long. Inert glass beads of 425-600 µm diameter (Sigma Aldrich) were placed upstream and downstream of the bed, extending the reactor configuration to 50 cm. The string of particles was held in place by a frit-in-a-ferrule filter (IDEX) at the outlet of the reactor. An important parameter in SPSRs is their low aspect ratio, defined as the ratio of the reactor diameter over the particle diameter, which is usually below 2 [284]. The average wet diameter of the catalyst, after swelling, was measured using a digital microscope (VHX-600, Keyence) to be 800 µm. This gave the reactor an aspect ratio of 1.25. Figure 4-1 shows images of the catalyst in a dry state. During the experiment, the particles swelled by approximately 6%, consistent with observations by Waldron et al. [51]. However, due to light refraction in the reacting medium, it was difficult to measure the swollen particles inside the reactor without distortion, as illustrated in Figure 4-2. To investigate internal mass transfer resistances, smaller Amberlyst-15 beads (500-600 µm) were loaded in a 0.75 mm ID PTFE tube (Agilent), maintaining a similar aspect ratio.

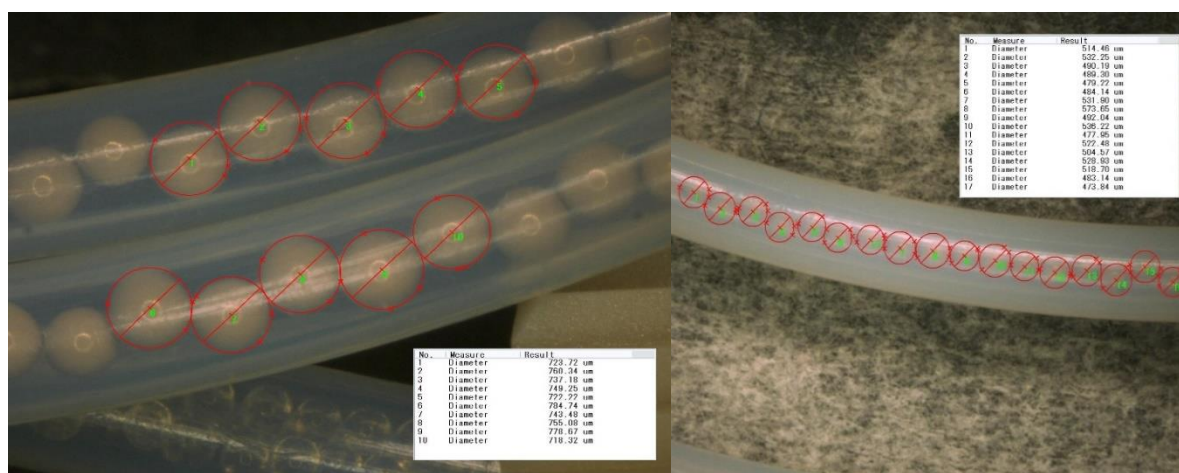


Figure 4-1. Microscope image of the dry Amberlyst-15 catalyst particles (a) from the 710-850 µm sieve fraction and (b) from the 500-600 µm sieve fraction.

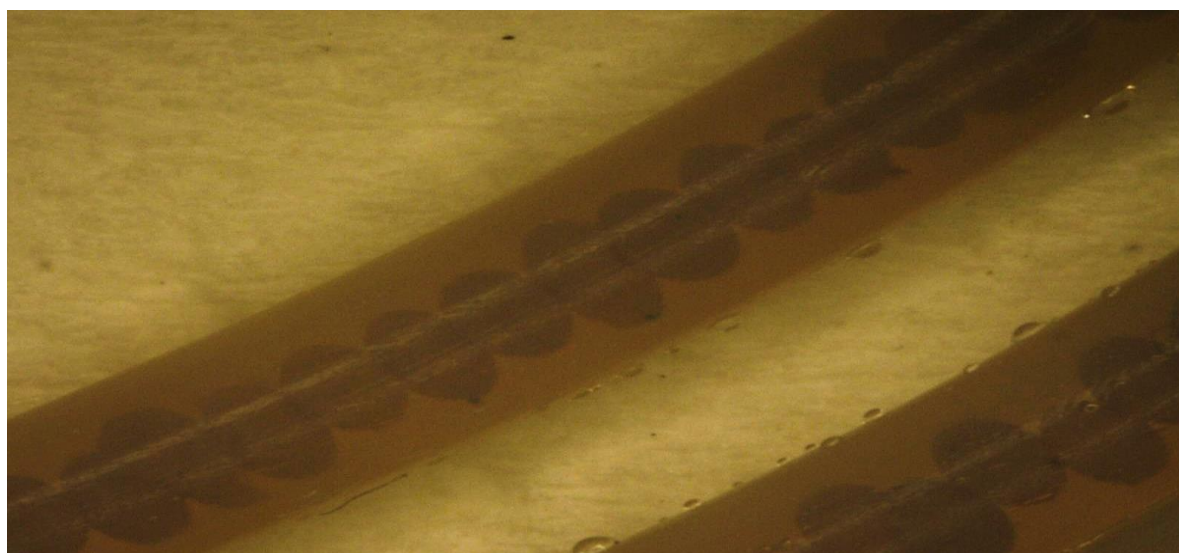


Figure 4-2. Image of the wet Amberlyst-15 beads.

4.2.2. Equipment and operation

A schematic of the set-up is shown in Figure 4-3. Two solutions of levulinic acid (98%, Sigma Aldrich) in ethanol ($\geq 99.8\%$, Sigma-Aldrich) with initial concentrations of 0.4 M and 2 M were prepared and each was loaded in a 10 mL stainless steel syringe (CETONI), mounted on a syringe pump (Nemesys medium-pressure module, CETONI). This enabled a range of feed concentrations by adjusting the relevant flowrates. The fluids were mixed at a T-junction of 1/16" O.D. and 0.020 thru hole (IDEX) before entering the SPSR. The reactor was submerged into a glycerol bath, which was continuously heated and stirred by a digital hotplate (IKA, RCT 5 digital). A temperature controller, connected to the hotplate, monitored and controlled the heating fluid temperature via a partially submerged thermocouple. The reactor outlet was connected to a six-way switching valve of a sampler-dilutor (Asia Sampler and Dilutor, Syrris) equipped with a mixing chip (Micromixer Chip, Dolomite) that sent the sample into a HPLC

chromatograph (LC-4000, Jasco) for the quantification of the levulinic acid and ethyl levulinate concentrations. Each experiment (i.e., different experimental conditions) ran for an hour, and every 6 min, a sample of 10 μL of the reactor's effluent was diluted online with the mobile phase that consisted of 60/40 acetonitrile/HPLC grade water (Sigma Aldrich) by a factor of 100 and was injected into the HPLC column (Thermo Fischer Scientific, Hypersil™ ODS C18) with a flowrate of 0.8 mL/min. The column oven was maintained at 40 °C and the detection was achieved using a UV-vis detector at 272 nm. The rest of the reaction mixture was continuously collected into a 100 mL stainless-steel pressure vessel (CRVZS-0.1, Festo). To prevent evaporation of the lower boiling components, the entire system was pressurised to 5 barg with nitrogen (BOC) using a mass flow controller (SLA mass flow controller, Brooks Instrument BV), a gas pressure sensor (Honeywell 40PC, 250 psig) and a back-pressure regulator (Swagelok K series, 250 psig), connected to the pressure vessel. The back pressure regulator ensured that the pressure in the pressure vessel was no lower than a certain value, while also working as a pressure relief valve, expelling excess gas. A liquid pressure sensor (Ashcroft G2500, 0-500 psi) was placed upstream the reactor entrance to measure the pressure drop in the reactor and two more pressure relief valves (IDEX U-456, 100psi) were installed after each syringe pump to ensure safe operation.

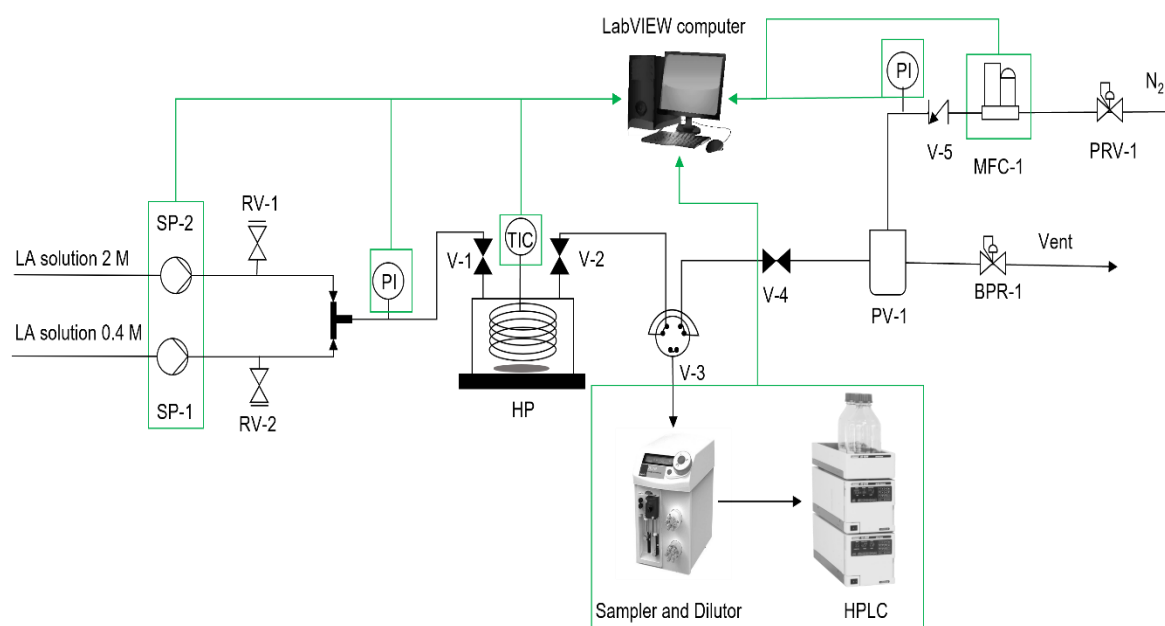


Figure 4-3. Automated platform used for the kinetic experiments of the esterification of levulinic acid (LA) to ethyl levulinate (EL) using Amberlyst-15 as a heterogeneous catalyst in a Single Pellet String reactor. Green lines indicate LabVIEW controlled or monitored equipment. SP: syringe pump, PRV: pressure reducing valve, RV: pressure relief valve, MFC: mass flow controller, PV: pressure vessel, PI: pressure indicator, BPR: back pressure regulator, V: valve, HP: hotplate, TIC: temperature indicator-controller, HPLC: high performance liquid chromatograph.

4.2.3. Automation

The experiments were fully automated using the Laboratory Virtual Instrument Engineering Workbench (LabVIEW) environment [276]. One of the benefits of employing LabVIEW is its compatibility with instrument drivers provided by numerous lab equipment manufacturers. Consequently, LabVIEW, along with its extensive library of instrument drivers, facilitates the seamless integration of multiple equipment components.

One common issue with automated systems is their specificity to particular tasks, which means that making even small adjustments to the experimental set-up can require a significant amount of effort to update the system, occasionally rendering manual experiments quicker [58]. However, the LabVIEW code developed in this context can be applied to various types of equipment, making it suitable for multiple reaction systems with only minor modifications. As a result, the same LabVIEW code is also used in Chapters 5 and 6 and continues to be a valuable resource for future projects within the Gavrilidis research group.

The LabVIEW code developed for this project, allowed the user to run a set of experiments by setting the temperature, feed concentration and total flowrate at the user interface panel (Appendix B, Section B6). Prior to conducting the experiments, the calibration curves, based on the area of the peaks for mixtures of levulinic acid and ethyl levulinate in ethanol at 272 nm, were created, which are displayed in Figure 4-4.

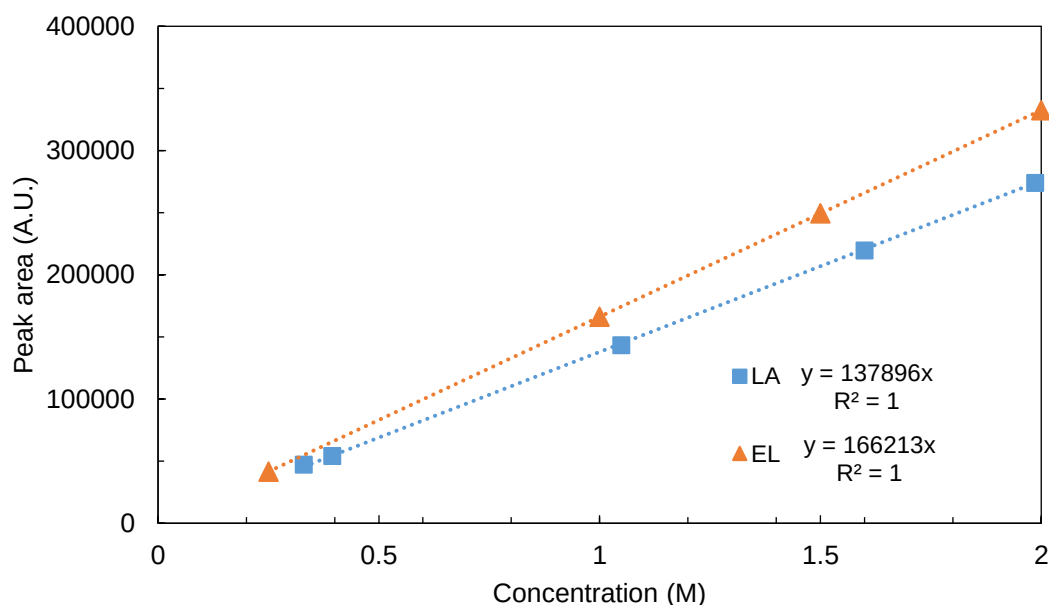


Figure 4-4. Calibration of the HPLC for mixtures of LA and EL in ethanol with a dilution factor of 100 with UV-vis detection at 272 nm.

Since there was no driver available for the HPLC system, using its own software (ChromNAV, Jasco) and a simple Python code, the results of the analysis were sent to an Excel file, where

LabVIEW was able to access and read them. In this way, the outlet concentrations of levulinic acid and ethyl levulinate were displayed at the end of each experimental condition. For visualisation purposes, the temperature and pressure trends of the system were also displayed in real time in graph charts and the software featured an overheating and overpressurisation safety limit, which were set to 120 °C (maximum operating temperature of Amberlyst-15) and 6 barg respectively and would automatically stop the experiment if these values were exceeded.

4.3. Procedure for screening of kinetic models¹

In kinetic model identification, the goal is to obtain a kinetic model that agrees with experimental data with precise estimation of the model parameters. To achieve this, the procedure followed in this work can be broken down in the steps, shown in Figure 4-5. A description of the steps is provided below and a detailed analysis can be found in the following subsections.

- 1) Determination of a reactor model: This step focuses on the mathematical description of the reactor used, taking into consideration external and internal mass transfer limitations.
- 2) Proposal of candidate kinetic models: Candidate kinetic models are proposed, which are either chosen from the literature or suggested by the user.
- 3) Design of experiments using DoE methods: If there is no prior information about the reaction, a traditional design of experiments is performed, using techniques such as Factorial Design (FD) or Latin Hypercube Sampling (LHS).
- 4) Execution of experiments and validation of the experimental platform: The automated reaction platform is used to carry out a list of pre-designed experiments provided by the user. To guarantee the platform's robustness and consistency in terms of control, a reproducibility check, as well as the estimation of the measurement error for each measurable response, are conducted.
- 5) Parameter estimation: Using statistical tools and the data produced from the execution of experiments, the parameters of all the proposed models are estimated.
- 6) Model discrimination using Lack of Fit statistics: The fitting quality of the models is evaluated using the χ^2 test. Any candidate model that fails the χ^2 test is automatically rejected.
- 7) Practical identifiability analysis on parameter estimates: In parallel with Step 6, the models are checked for the uncertainty in the estimation of their parameters by

¹ The statistical analysis of Chapter 4 was completed with the support of Ms. Märthe Theresa Tillmann from the Faculty of Mechanical Engineering, RWTH Aachen University.

conducting an identifiability study. If the models pass both the chi-square (χ^2) test and all their parameters are identifiable, the procedure is complete. If the models' parameters are unidentifiable, a reformulation of the candidate kinetic models is proposed, and the procedure returns to Step 5.

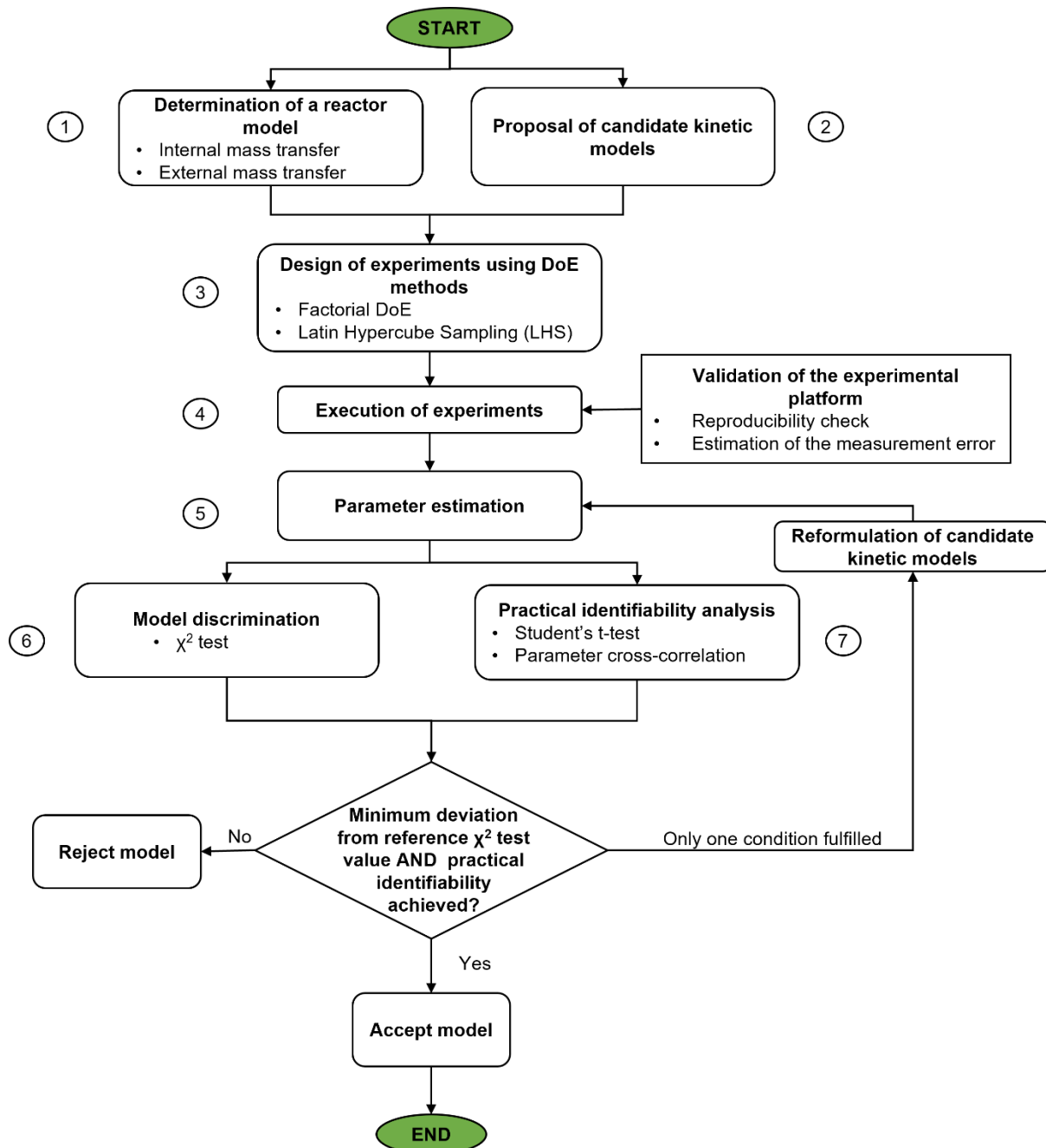


Figure 4-5. Flowchart of the general methodology proposed for kinetic model identification.

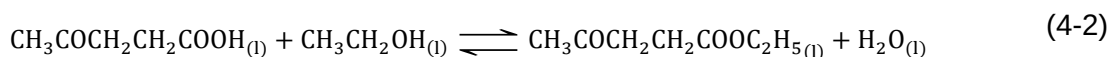
4.3.1. Determination of a reactor model

The reactor model is a mathematical representation of the chemical reactor system. By applying principles of mass and energy conservation and incorporating reaction kinetics, it provides the concentration profiles of the various components along the reactor. Based on residence time distribution studies reported previously for a similar system [69], axial dispersion can be neglected. The reactor used in this study is modelled as an ideal plug flow reactor with catalyst amount as the integration variable according to Equation 4-1, where m_{A15} is Amberlyst-15 mass (g), r'_{LA} is the rate of reaction of levulinic acid per mass of catalyst (mol g⁻¹ s⁻¹) and Q_0 is the inlet liquid flowrate (L/s). Due to the size of Amberlyst-15 used, there was an indication of existence of internal mass transfer resistances [366]. Therefore, the reaction rate in Equation 4-1 concerns apparent kinetics, as also verified in Section 4.1. The initial concentration of LA in the feed, temperature and total flowrate are the control experimental variables for a constant mass of catalyst, with the concentration of LA and EL measured at the outlet of the reactor.

$$\frac{dC_{LA}}{dm_{A15}} = -\frac{r'_{LA}}{Q_0} \quad (4-1)$$

4.3.2. Proposal of candidate kinetic models

Kinetic models for liquid systems express the reaction rate as a function of concentration and temperature. For the reaction of interest, displayed in Equation 4-2, candidate kinetic models are proposed (Table 4-1) and discriminated systematically at a later stage (Sections 4.6 and 4.7), as suggested by Steps 6 and 7 of Figure 4-5. These models can be derived based on the available information and assumptions made. The list of candidate kinetic models includes not only mechanistic models, which represent the potential underlying chemistry and have consistent physical basis, but also reformulated mechanistic models that can be called 'semi-empirical' (i.e., in the case of low affinity of the reaction components with the catalyst, the adsorption equilibrium constants were neglected), where re-parametrisation techniques have been applied [372, 373] to avoid practically unidentifiable kinetic parameters in the examined design space.



The reaction mechanism for the esterification of levulinic acid with ethanol over an ion-exchange resin, as illustrated in Figure 4-6, could be described as a Fischer esterification. can be described as a Fischer esterification. Typically, a Fischer esterification is performed in the

presence of a Brønsted acid to catalyse the condensation of carboxylic acids and alcohols [374]. In the case of Amberlyst-15, the process is driven by presence of sulfonic acid groups, which serve as the active sites that kick-start the proton donation to the carboxylic acid [375-377]. First, levulinic acid is adsorbed onto the catalyst surface, where it undergoes protonation, resulting in a protonated levulinic acid intermediate that increases the electrophilicity of the carbonyl carbon. After protonation, the carboxylic acid becomes more susceptible to a nucleophilic attack by the hydroxyl group of ethanol that leads to the formation of an oxonium ion. Following a proton transfer within the oxonium ion, a new oxonium ion is produced. In the final step, ethyl levulinate is formed through the loss of water followed by a deprotonation step, regenerating the sulfonic acid group on the catalyst surface [336]. The water present in the liquid phase can also participate in an exchange equilibrium with the sulfonic acid. Similarly, alcohol molecules can act as weak bases and accept protons from the sulfonic acid [375].

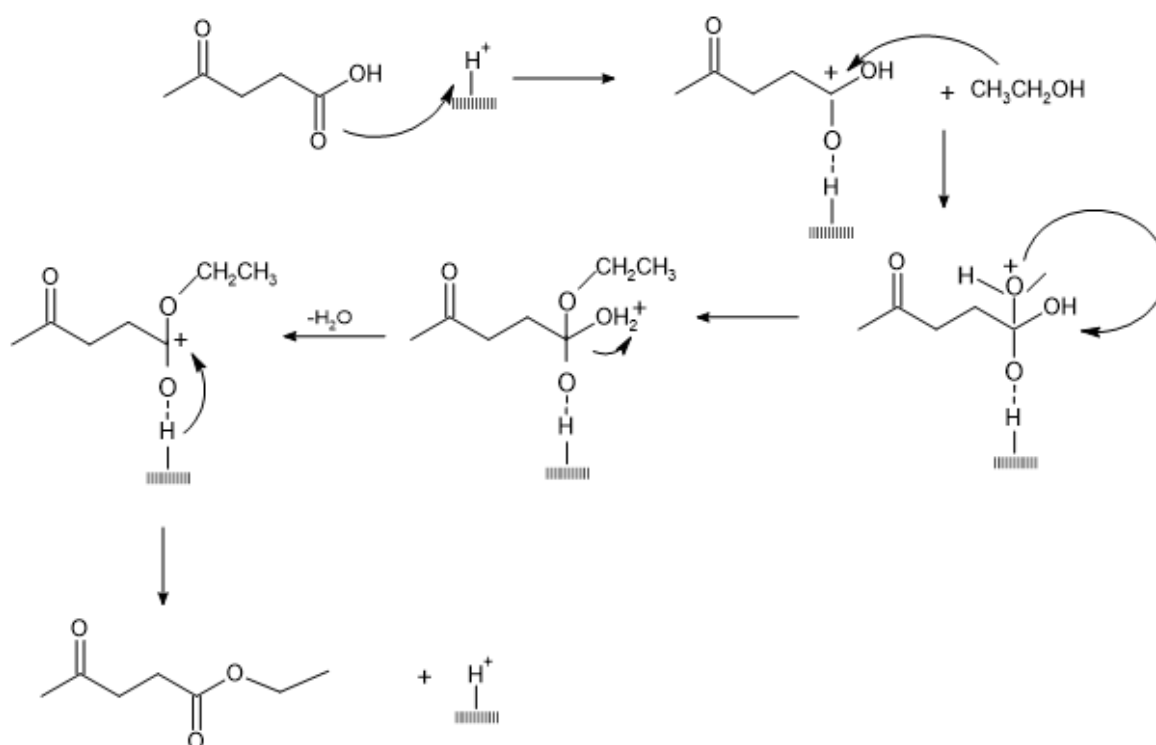


Figure 4-6. Fischer esterification reaction mechanism between levulinic acid and ethanol over Amberlyst-15.

Unlike homogeneous catalytic systems, esterification reactions with heterogeneous solid acid catalysts, such as Amberlyst-15, involve several steps (adsorption, desorption, pore diffusion, reaction) that happen either in parallel or sequentially, thus rendering the overall reaction mechanism (and the respective reaction rate) complex. Due to the complex interaction of the species with the catalyst active sites, esterification reactions can be described using different approaches, including pseudo-homogeneous models as well as the adsorption-based

Langmuir-Hinshelwood-Hougen-Watson (LHHW) and Eley-Rideal (ER) models. Candidate kinetic rate expressions, based on mechanistic models, were found in literature for similar esterification systems, which, as well as other proposed formulations inspired by those, were considered, as shown in Table 4-1. The main assumptions for all the models investigated were the following: a) The reaction was considered irreversible, due to the large excess of ethanol used (molar ratio greater than 9:1). b) The reaction on the catalytic sites was the rate-limiting step for ER and LHHW models considering adsorption, reaction and desorption as elementary steps. c) Autocatalysis was not included in the kinetic expressions, as it was proven negligible for the conditions studied, as explained in Section 4.4. d) The reaction mixture behaved ideally; hence, concentrations were used in the reaction rate expressions instead of activities. e) The reaction temperature was assumed equal to the measured temperature of the heating fluid. f) The concentration of the different species on the catalyst surface was equal to the concentration in the bulk fluid, as there were no external mass transfer resistances (See Appendix B).

Table 4-1. Kinetic models screened for the esterification reaction. The tickmarks indicate the corresponding species adsorption equilibrium constant being present in the mathematical formulation of the LHHW (models 3-17) or ER expressions (models 18-28). Missing tickmarks are therefore referring to species for which the interaction with the catalyst is not modelled, be it because of practical unidentifiability of the parameter or because adsorption of the species is not occurring in the respective mechanism. EtOH: ethanol, LA: levulinic acid, EL: ethyl levulinate and W: water.

Reaction mechanism	Model	Rate expression / Adsorption of relevant component considered				Description
		EtOH	LA	EL	W	
Pseudo-homogeneous	1	$r'_{LA} = kC_{LA}C_{EtOH}$				No adsorption on the catalytic sites [366]
	2	$r'_{LA} = kC_{LA}^2$				Second order with respect to levulinic acid [343]
Langmuir-Hinshelwood-Hougen-Watson	$r'_{LA} = \frac{kC_{LA}C_{EtOH}}{(1 + K_{LA}C_{LA} + K_{EtOH}C_{EtOH} + K_{EL}C_{EL} + K_W C_W)^2}$					
	3	✓	✓	✓	✓	Surface reaction between adsorbed LA and adsorbed EtOH with all species participating in the reaction rate expression [378]

	4	✓	✓		✓	Weak EL adsorption (proposed)
	5	✓	✓	✓		Weak H ₂ O adsorption (proposed)
	6	✓	✓			Fast product desorption (proposed)
	7		✓	✓	✓	Weak EtOH adsorption (proposed)
	8		✓		✓	Weak EtOH and EL adsorption [379]
	9		✓	✓		Weak EtOH and H ₂ O adsorption (proposed)
	10		✓			Strong LA adsorption (proposed)
	11	✓		✓	✓	Weak LA adsorption (proposed)
	12	✓			✓	Weak LA and EL adsorption [379]
	13	✓		✓		Strong EtOH and EL adsorption (proposed)
	14	✓				Strong EtOH adsorption (proposed)
	15			✓	✓	Strong adsorption of products (proposed)
	16				✓	Strong H ₂ O adsorption (proposed)

	17			✓		Strong EL adsorption (proposed)
Eley-Rideal	$r'_{LA} = \frac{kC_{LA}C_{EtOH}}{1 + K_{LA}C_{LA} + K_{EL}C_{EL} + K_W C_W}$					
	18		✓	✓	✓	Surface reaction between adsorbed LA and bulk EtOH with competitive adsorption of the products (proposed)
	19		✓		✓	Strong LA and H ₂ O adsorption [380]
	20		✓	✓		Strong LA and EL adsorption (proposed)
	21		✓			Strong LA adsorption (proposed)
	$r'_{LA} = \frac{kC_{LA}C_{EtOH}}{1 + K_{EtOH}C_{EtOH} + K_{EL}C_{EL} + K_W C_W}$					
	22	✓		✓	✓	Surface reaction between adsorbed EtOH and bulk LA with competitive adsorption of the products (proposed)
	23	✓			✓	Strong EtOH and H ₂ O adsorption [381]
	24	✓		✓		Strong EtOH and EL adsorption [382]

25	✓				Strong EtOH adsorption (proposed)
26			✓	✓	Strong product adsorption (proposed)
27				✓	Strong H ₂ O adsorption (proposed)
28			✓		Strong EL adsorption (proposed)

For the LHHW and ER-inspired models the kinetic rate constant, k , is lumped with the relevant adsorption equilibrium constants of the reactants, as this reduces correlation between the parameters [260]. In all cases, the kinetic rate constant, k , is expressed in the re-parameterised Arrhenius form with parameters KP_1 and KP_2 for the pre-exponential factor, A , and the activation energy, E_α (Equations 4-3, 4-4 and 4-5).

$k = A e^{-\frac{E_\alpha}{RT}}$	(4-3)
$A = e^{-KP_1 + \frac{KP_2 \cdot b}{R \cdot T_M}}$	(4-4)
$E_\alpha = KP_2 \cdot b$	(4-5)

Here, T is the reaction temperature (K), b is a scaling factor equal to 10,000, and T_M is the reference temperature (K), which in this work, is equal to 85 °C, calculated as the average value of the upper and lower temperature limits of the experimental conditions tested.

For both LHHW and ER inspired models, the interaction of the solid ion-exchange resin with the liquid reactants is accounted for by the adsorption constant terms, K_{LA} , K_{EtOH} , K_W and K_{EL} present in the rate expressions, which are parameters to be estimated. For the esterification of levulinic acid with ethanol over Amberlyst-15, limited and often contradicting information is found regarding the adsorption strength of the investigated components on the catalyst sites [341, 366] and no data is available regarding the range of the adsorption constants and their dependency on the reaction temperature. Adsorption experiments on the esterification of acetic acid with methanol revealed that the adsorption affinity of the reaction's components onto Amberlyst-15 was augmented according to their polarity and was dependent on

temperature [383]. Therefore, water, as one of the products, was expected to adsorb the strongest on the catalyst. Similarly to the mathematical formulation of the reaction rate constant, the adsorption equilibrium constant for each species, K_i (m^3/mol), can be expressed as shown in Equation 4-6 to 4-8, where a re-parameterised form of the Van't Hoff equation, with parameters $KP_{\text{ads}1,i}$ and $KP_{\text{ads}2,i}$, is used to reduce the correlation between the adsorption equilibrium constant at the reference temperature, $K_{i,\text{ref}}$ and the relative enthalpy of adsorption ΔH_i .

$$K_i = K_{i,\text{ref}} e^{-\frac{\Delta H_i}{R}(\frac{1}{T} - \frac{1}{T_M})} \quad (4-6)$$

$$K_{i,\text{ref}} = e^{-KP_{\text{ads}1,i} + \frac{KP_{\text{ads}2,i} \cdot b}{R \cdot T_M}} \quad (4-7)$$

$$\Delta H_i = KP_{\text{ads}2,i} \cdot b \quad (4-8)$$

4.3.3. Design of experiments using DoE methods

A general reaction system model, comprising the reactor model as well as the kinetic model, as explained in Sections 4.3.1 and 4.3.2, is represented by a set of differential and algebraic equations (DAEs), the solution of which characterises the modelled system behaviour.

$$\begin{aligned} \mathbf{f}(\dot{\mathbf{x}}(\mathbf{t}), \mathbf{x}(\mathbf{t}), \mathbf{u}(\mathbf{t}), \boldsymbol{\theta}) &= \mathbf{0} \\ \hat{\mathbf{y}} &= \mathbf{g}(\mathbf{x}(\mathbf{t}), \mathbf{u}(\mathbf{t}), \boldsymbol{\theta}) \end{aligned} \quad (4-9)$$

In Equation 4-9, $\mathbf{x}$ is the N_x dimensional vector of the state variables, $\dot{\mathbf{x}}$ is the vector of first derivatives of the state variables, $\mathbf{u}$ is the N_u dimensional vector of inputs or control variables, defined by the experimental conditions, $\boldsymbol{\theta}$ is the N_θ dimensional vector of the kinetic model parameters and $\hat{\mathbf{y}}$ is the $N_{\hat{y}}$ vector of model predictions of the outputs or measurable responses, $\mathbf{y}$. The vector of functions representing the state equation is denoted as $\mathbf{f}$, and $\mathbf{g}$ denotes a function selecting the set of state variables representing measured outputs, both being usually nonlinear functions of $\boldsymbol{\theta}$ and $\mathbf{u}$ for chemical reaction systems [71].

In this study, $\mathbf{x}$ comprises the concentrations of levulinic acid (C_{LA}), ethanol (C_{EtOH}), ethyl levulinate (C_{EL}) and water (C_{W}), $\mathbf{u}$ comprises the reaction temperature, the feed concentration and the total flowrate, $\boldsymbol{\theta}$ includes model parameters, namely KP_1 and KP_2 (i.e., re-parametrised pre-exponential factor (A) and energy of activation (E_α) (Equations 4-3 to 4-5) and constant values of K_i (for the case of temperature-independent models) or $KP_{\text{ads}1,i}$ and $KP_{\text{ads}2,i}$ (when temperature dependency is considered) as re-parametrised values for the enthalpy of adsorption of the i different species (Equations 4-6 to 4-8). Data collected from different experimental conditions are represented by the experimental design vector $\boldsymbol{\phi}$, as shown in Equation 4-10.

$$\boldsymbol{\varphi} = [\mathbf{x}^{0T}, \mathbf{u}^T, m_{A15}]^T \quad (4-10)$$

In Equation 4-10, $\mathbf{x}^0$ is the initial state vector consisting of the experimental conditions and the amount of catalyst, m_{A15} . The design space $\mathbf{D}$ includes all possible variants of experimental conditions and it is bounded by physical constraints of the experimental set up. For data collected by executing N_{exp} experiments and measuring N_y responses at steady state, the measurement response matrix $\mathbf{y}$ with dimensions $N_{\text{exp}} \times N_y$ can be defined.

Design of experiments (DoE) methods are statistical sampling techniques that are used to achieve process knowledge, through the establishment of mathematical relationships between process inputs and outputs [384]. Computationally cheap designs such as full or fractional Factorial Design (FD) [385] or Latin Hypercube Sampling (LHS) [386] are employed. Since there was limited information available about the reaction, a factorial design at two-levels was used, which resulted in a total of eight experimental conditions.

Two different sets of experiments were carried out. A preliminary set of experimental conditions, denoted as Experimental Set 1, included the variation of the reaction temperature, total inlet flowrate and inlet concentration of LA between the upper and lower limits. A more refined set of experiments, indicated as Experimental Set 2, was conducted with the only difference from Experimental Set 1 being the introduction of water in the feed solution at a concentration of 4 M, which fell within the solubility limits of LA in water (Appendix B, Section B3) and also guaranteed that no equilibrium was reached even at the highest temperature, based on the reaction equilibrium constant [345] (Appendix B, Section B4). The reason behind the introduction of water lies in challenges associated with the distinguishability of models in the design space of Set 1, as both products are produced in equal concentrations according to the reaction stoichiometry. A detailed explanation on the influence of the design space is provided in Section 4.4.2.

The lower and upper limits of the input variables considered for the factorial experiments, are presented in Table 4-2 and the design space is illustrated in Figure 4-7. The bounds chosen were dictated by constraints in the experimental platform. Residence times were constrained to the accuracy range of the syringe pumps, which applied pressure on 10 mL stainless steel syringes, dispensing through the system under 5 barg backpressure. The maximum flowrate allowed was set at 60 $\mu\text{L}/\text{min}$ to prevent the syringes emptying too quickly and a minimum flowrate of 20 $\mu\text{L}/\text{min}$ was chosen to keep the residence time small enough that an experiment could be completed in a reasonable amount of time, whereas the temperature range was

determined based on heating/cooling ability of the system and the maximum operational temperature of Amberlyst-15, set at 120 °C.

Table 4-2. Experimental control variable ranges used in this work.

	Set 1		Set 2	
Control variable	Lower limit	Upper limit	Lower limit	Upper limit
Temperature (°C)	70	100	70	100
Total flow rate (μL/min)	20	60	20	60
Inlet concentration of LA (M)	0.8	1.6	0.8	1.6
Inlet concentration of water (M)	-	-	4	4

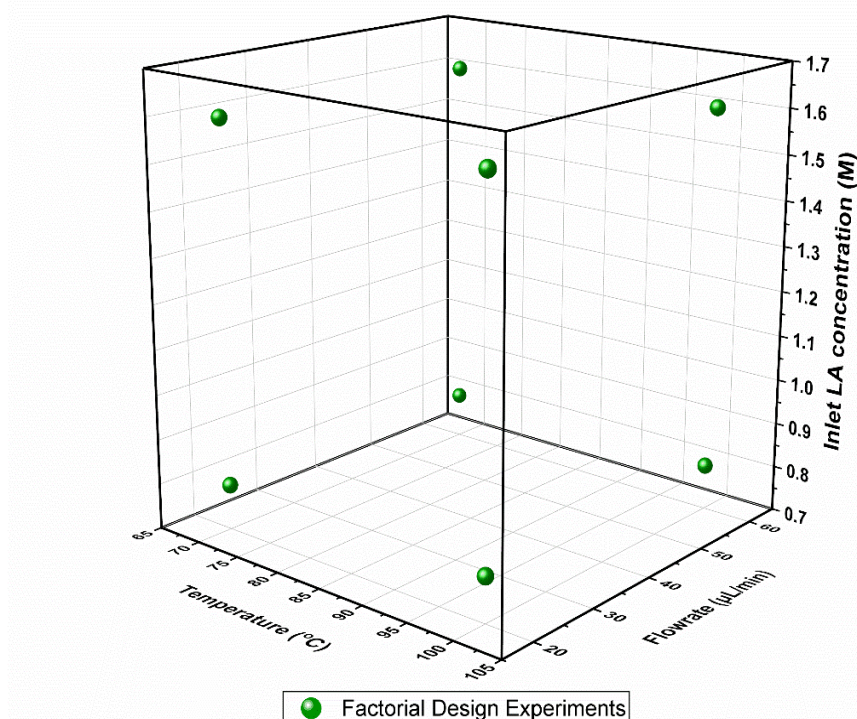


Figure 4-7. Experimental conditions of the reaction experiments, designed by the factorial method.

4.3.4. Execution of experiments and validation of the experimental platform

For the adopted conditions, it was demonstrated by NMR spectroscopy (see Appendix B) that no side reactions were taking place. Moreover, given the autocatalytic nature of the reaction, which results in maximum 7% conversion at 90 °C after 5.5 hours of batch experiments [345], the presence of homogenous reaction was investigated in the maximum temperature and lowest flowrate in an empty reactor of similar length. It was proven that the amount of ethyl levulinate produced was negligible and could not be quantified by liquid chromatography.

The campaign was conducted in three replicates. On two consecutive days, the experimental platform was set-up, and the reactor ran for 8 hours without interference, thus allowing to establish robustness of the system. The reproducibility of the system and the calculation of

the measurements' variance were achieved by repeating the experimental conditions in an identical, freshly packed reactor. To estimate the measurement error, it is assumed that the N_y measured responses (in this work, the measured responses are two, the concentration of LA (C_{LA}) and EL (C_{EL})) of a true model are corrupted with uncorrelated normally distributed measurement error with zero mean vector and standard deviation σ_j . Therefore, the measurement error is expressed as $N_y \times N_y$ dimensional covariance matrix Σ with σ_j^2 as entries on the diagonal. Furthermore, the error is attributed solely on the system response variables and not on systematic bias or error from other sources like imperfect input control and thus assumed to be constant over the entire design space of a dataset. The standard deviation of the measurement error for levulinic acid concentration was calculated to be 0.012 M for Experimental Set 1 and 0.021 M for Experimental Set 2. For ethyl levulinate concentration, the standard deviation was 0.015 M for Experimental Set 1 and 0.012 M for Experimental Set 2. For the combined data from Sets 1 and 2, the standard deviation of the measurement error for each measured response was taken as the maximum value from the respective sets.

4.3.5. Parameter estimation

Parameter estimation concerns the identification of values for the unknown parameters θ in the kinetic expression. These values are the solution of an optimisation problem that involves the minimisation of lack of fit expressed as a function of the residuals ϵ_i . The vector of residuals ϵ_i is the difference between model prediction $\hat{y}_i$ and the measured model response y_i for the i -th experiment for the N_y measurement variables (Equation 4-11). In this work, a chi-square (χ^2) test has been used as statistical hypothesis test to quantify and compare the Lack of Fit (LoF) of candidate kinetic models. The LoF was assessed using the χ^2 value calculated as the weighted sum of squared of the residuals ϵ_i (Equation 4-12) obtained after maximum likelihood parameter estimation. The χ^2 value is a function of the kinetic parameters vector, θ , and is minimised at the optimal parameter estimates, $\hat{\theta}$. Moreover, the χ^2 value is also used for model discrimination described in Section 4.3.6.

$$\epsilon_i = \hat{y}_i - y_i \quad \forall i = 1, \dots, N_y \quad (4-11)$$

$$\chi^2 = \sum_{i=1}^{N_{\text{exp}}} \sum_{j=1}^{N_y} \Sigma_{j,j}^{-1} \cdot \epsilon_{i,j}^2 \quad (4-12)$$

4.3.6. Model discrimination using Lack of Fit statistics

Differences in the fitting of several models are evaluated by comparing their LoF using the χ^2 value [259, 387] (Equation 4-12). The LoF of each model is compared against a threshold value, also known as reference value, χ_{ref}^2 , which is the χ^2 value of the χ^2 distribution with $N_{\text{exp}} \cdot N_y - N_{\theta}$ degrees of freedom (DoF) and a certain confidence level [388] (here 95%). In the context of this study, a less stringent criterion for the LoF was implemented, where models exhibiting a lower χ^2 in comparison to other candidate models were still considered as potential models, even if their χ^2 exceeded the threshold value. This relaxation of the LoF condition was motivated by the overarching objective of identifying the optimal approximating model from the pool of screened candidates.

4.3.7. Practical identifiability analysis on parameter estimates

As parameter estimates are the product of model fitting to experimental data effected by a measurement error, Σ , parameter estimates are uncertain. The uncertainty is quantified by the $N_{\theta} \times N_{\theta}$ dimensional variance-covariance matrix of parameter estimates, $\hat{\mathbf{V}}_{\theta}$ that is a common measure of the parameter estimates' precision, defined as the inverse of the observed Fisher information matrix $\hat{\mathbf{H}}_{\theta}$ [264].

$$\hat{\mathbf{V}}_{\theta}(\hat{\theta}) \cong [\hat{\mathbf{H}}_{\theta}(\hat{\theta})]^{-1} = \left[[\hat{\mathbf{V}}_{\theta}^0]^{-1} + \sum_{i=1}^{N_{\text{exp}}} \hat{\mathbf{S}}^T(\boldsymbol{\varphi}_i, \hat{\theta}) \Sigma^{-1} \hat{\mathbf{S}}(\boldsymbol{\varphi}_i, \hat{\theta}) \right]^{-1} \quad (4-13)$$

In Equation 4-13, $\hat{\mathbf{V}}_{\theta}^0$ is the a-priori covariance matrix of the model parameters calculated from the potential prior knowledge of parametric space (in this study, it was a null matrix as there was no preliminary information provided), $\hat{\mathbf{S}}(\boldsymbol{\varphi}_i, \hat{\theta})$ represents the linear approximation for the sensitivity of model predictions $\hat{\mathbf{y}}$ with respect to model parameters $\hat{\theta}$. For experiment i , $\hat{\mathbf{S}}$ is defined as a $N_y \times N_{\theta}$ dimensional matrix as follows.

$$\hat{\mathbf{S}}(\boldsymbol{\varphi}_i, \hat{\theta}) = \begin{pmatrix} \frac{\partial \hat{y}_{i,1}(\hat{\theta})}{\partial \hat{\theta}_1} & \dots & \frac{\partial \hat{y}_{i,1}(\hat{\theta})}{\partial \hat{\theta}_{N_{\theta}}} \\ \vdots & \ddots & \vdots \\ \frac{\partial \hat{y}_{i,N_y}(\hat{\theta})}{\partial \hat{\theta}_1} & \dots & \frac{\partial \hat{y}_{i,N_y}(\hat{\theta})}{\partial \hat{\theta}_{N_{\theta}}} \end{pmatrix} \quad \forall i = 1, \dots, N_{\text{exp}} \quad (4-14)$$

Parameter correlation can be quantified from the parameter correlation matrix $\mathbf{C}$ for which the entry of row i and column j is calculated based on the entries of the variance-covariance matrix of parameter estimates $\hat{\mathbf{V}}_{\theta}$, as shown in Equation 4-15.

$$C_{i,j} = \frac{\hat{V}_{\theta_{i,j}}}{\sqrt{\hat{V}_{\theta_{i,i}}}\sqrt{\hat{V}_{\theta_{j,j}}}} \quad \forall i, j = 1, \dots, N_{\theta} \quad (4-15)$$

From the parameter variance-covariance matrix $\hat{V}_{\theta}$, the linear Confidence Interval (CI) for the i -th parameter $\hat{\theta}_i$ is computed as follows [389].

$$CI_i = \sqrt{\hat{V}_{\theta_{i,i}}} \cdot t_2(p - \text{value}, \text{DoF}) \quad \forall i = 1, \dots, N_{\theta} \quad (4-16)$$

with $t_2(p - \text{value}, \text{DoF})$ being the t -value of a two-tailed Student's t -distribution dependent on user defined significance level (here 5%) and the $N_{\text{exp}} \cdot N_y - N_{\theta}$ degrees of freedom (DoF) of the model. The t -value of each parameter is defined as the ratio of the parameter estimate over the CI.

$$t_i = \frac{|\hat{\theta}_i|}{CI_i} \quad \forall i = 1, \dots, N_{\theta} \quad (4-17)$$

The significance of the parameter estimate can be evaluated through the statistical Student's t -test. The value of the parameter estimated by Equation 4-17 is compared to a reference t -value from a Student's t -distribution with the $N_{\text{exp}} \cdot N_y - N_{\theta}$ DoF and a significance level. If the t -value of a parameter is lower than the reference t -value, this usually indicates that the parameter is estimated poorly [16]. Moreover, high correlation of parameter estimates, $C_{i,j}$, and a comparable low order of magnitude of a parameter estimate are criteria for unidentifiability [364]. In the present work models are classified as practically identifiable if all parameter estimates and all t -values are higher than 0.01, for a significance level of 5%, and the parameter cross correlation, $C_{i,j}$, does not exceed 0.995. If at least one of the criteria is not met, the models are considered unidentifiable.

4.4. Results and discussion

4.4.1. Estimation of external and internal mass transfer resistance

4.4.1.1. External mass transfer resistance

Within the overall objective to identify kinetics for the esterification of levulinic acid with ethanol, it was required to check if the rate of liquid-solid mass transfer was sufficiently high so that it could be neglected from the kinetic model. The external mass transfer can be assessed using the Mear's criterion [90].

$$\frac{-r'_{LA} \rho_b r_p n}{k_{LS} C_{LA,bulk}} < 0.15 \quad (4-18)$$

where r'_{LA} is the rate of mass transfer of levulinic acid per mass of catalyst ($\text{kmol} \cdot \text{s}^{-1} \cdot \text{kg}^{-1}$), ρ_b is the bulk density of catalyst ($\text{kg} \cdot \text{m}^{-3}$), r_p is the radius of the catalyst particle (m), n is the reaction order, k_{LS} is the liquid-solid mass transfer coefficient ($\text{m} \cdot \text{s}^{-1}$) and $C_{LA,bulk}$ is the concentration of levulinic acid in the bulk solution ($\text{kmol} \cdot \text{m}^{-3}$).

Using the high temperature experimental data shown in Table B-1 and Table B-2 of the Supporting Information, the rate of reaction per mass of catalyst is approximated as the average rate of reaction along the length of the string reactor using

$$r'_{LA} = \frac{Q_0 \cdot (C_{LA,in} - C_{LA,out})}{m_{A15}} \quad (4-19)$$

where Q_0 is the inlet volumetric flowrate (m^3/s), $C_{LA,in}$ and $C_{LA,out}$ are the concentrations of levulinic acid at the inlet and outlet respectively (mol/m^3) and m_{A15} is the mass of catalyst (g). The conditions studied and the observed rate of reaction are shown in Table 4-3. In all cases, the observed rate of reaction was found to be $< 8.98 \cdot 10^{-6} \text{ kmol} \cdot \text{s}^{-1} \cdot \text{kg}^{-1}$.

Table 4-3. Observed rate of reactions for high temperature experimental data.

Experiment	Temperature (°C)	Flowrate (μL/min)	Inlet LA concentration (M)	r'_{LA} ($\text{kmol} \cdot \text{s}^{-1} \cdot \text{kg}^{-1}$)
5	100	20	0.8	2.42E-06
6	100	20	1.6	4.57E-06
7	100	60	0.8	4.88E-06
8	100	60	1.6	8.98E-06

The bulk catalyst density was calculated according to Equation 4-20

$$\rho_b = \rho_c(1 - \varepsilon) \quad (4-20)$$

where ρ_c is the pellet catalyst density (kg/m^3), and ε is the void fraction of the string reactor.

According to the manufacturer specifications [390], the pellet catalyst density is $610 \text{ kg} \cdot \text{m}^{-3}$ and the bed porosity was calculated to be 0.535 for a string reactor of $1000 \text{ } \mu\text{m}$ diameter packed with $800 \text{ } \mu\text{m}$ spheres [391]. The bulk catalyst density in the reactor was then calculated to be equal to $283.65 \text{ kg}/\text{m}^3$.

The solid-to-liquid mass transfer coefficient for SPSRs, was calculated based on the global correlation for the estimation of mass transfer coefficient developed in Chapter 3 (Equation 3-39).

The Wilke-Chang equation, Equation 4-21, was used to estimate the value of molecular diffusivity in $\text{cm}^2\cdot\text{s}^{-1}$

$$D_m = \frac{7.4 * 10^{-8}(\varphi MW)^{0.5}T}{\mu_L V_{\text{molar}}^{0.6}} \quad (4-21)$$

where subscripts 1 and 2 are for the solute and solvent respectively, φ is the association parameter of the solvent, which is 1.5 for alcohols, MW is the molecular weight (g/mol), μ_L is the dynamic viscosity (cP), V_{molar} is the molar volume (mL/mol) and T is the temperature (K). For levulinic acid in ethanol the molecular weight of the solvent is 46.07 g/mol, the molar volume of levulinic acid is 129.37 mL/mol [392].

For the calculation of dynamic viscosity, we considered that the reacting mixture has the properties of the solvent, ethanol, and therefore, the Vogel equation was used, where T is temperature in Kelvin and with parameters taken from the Dortmund Data Bank.[393]

$$\mu_L = \exp \left(-7.3714 + \frac{2770}{74.6787 + T} \right) \quad (4-22)$$

The ethanol liquid density was calculated based on the DIPPR105 equation with parameters taken by Dortmund Data Bank, based on the work of Golubev et al.[394]

$$\rho = \frac{99.3974}{0.310729^{1+(1-\frac{T}{513.18})^{0.305143}}} \quad (4-23)$$

The values of the dimensionless numbers for the conditions studied, Sc, Re and Sh, as well as the k_{LS} and value of the Mear's criterion (assuming a first order reaction) are shown in Table 4-4.

Table 4-4. Calculated values of dimensionless numbers and Mear's criterion parameter.

Experiment	Sc	Re_h	Sh	k_{LS} (m^2/s)	Mear's criterion parameter (-)
5	109.22	0.52	18.96	9.43E-05	0.004
6	109.22	0.52	18.96	9.43E-05	0.003
7	109.22	1.56	25.14	1.25E-04	0.006
8	109.22	1.56	25.14	1.25E-04	0.005

The dimensionless parameter of Mear's criterion for the existence of internal mass transfer was calculated to be significantly less than 0.15, hence suggesting that external mass transfer can be ignored.

4.4.1.2. Internal mass transfer resistance

Amberlyst-15 is a strongly acidic, macroreticular polymeric resin, prepared by the sulfonation of styrene copolymers cross-linked with divinylbenzene [367]. The macroreticular pore structure of Amberlyst-15 that contains both gel and non-gel porosity [368] permits access of liquid or gaseous reactants to its active sites found throughout the bead [395]. Due to the complex internal structure of Amberlyst-15, internal mass transfer resistances shall be taken into consideration, when investigating reaction kinetics. Russo et al. [366] demonstrated the presence of intraparticle diffusion limitations for the larger Amberlyst-15 particles, by examining spheres of average diameter of 600 and 300 μm , for the ethyl levulinate synthesis. The sizes obtained in this work when sieving the catalyst and loading the reactor were 755 μm and 550 μm , which due to swelling by 6%, resulted in diameters of 800 μm and 580 μm , respectively. Internal mass transfer resistances inside the large catalyst sphere were assessed using the Weisz-Prater criterion (Equation 4-24), assuming a first order reaction [90].

$$C_{WP} = \frac{-r'_{LA} \rho_c r_p^2}{D_e C_{LA,s}} \quad (4-24)$$

where ρ_c is the catalyst particle density (kg/m^3), r_p is the radius of the catalyst particle (m), $C_{LA,s}$ is the concentration of levulinic acid at the catalyst surface (mol/m^3) and D_e is the effective diffusivity of levulinic acid in the catalyst particle (m^2/s), which is calculated according Equation 4-25.

$$D_e = \frac{D_m \varepsilon_p \sigma_c}{\lambda} \quad (4-25)$$

Where, ε_p is the catalyst pellet porosity, σ_c is the constriction factor and λ is the catalyst tortuosity and the molecular diffusivity of levulinic acid in the ethanol solvent, D_m is calculated based on Equation 4-21. Since the external mass transfer resistances can be neglected, the concentration of levulinic acid at the catalyst surface, $C_{LA,s}$ can be approximated with the concentration of levulinic acid at the bulk solution, $C_{LA,bulk}$. The catalyst pellet porosity ε_p was taken equal to 0.32, the constriction factor σ_c value was equal to 0.8 and the tortuosity τ was taken equal to 3 [396].

Replacing the values into Equations 4-24 and 4-25, the Weisz-Prater parameter was then calculated for all experimental condition, as reported in Table 4-5.

Table 4-5. Weisz-Prater criterion, C_{WP} for the estimation of internal mass transfer resistances in Amberlyst-15 for the experimental conditions studied in this work.

Experiment	Temperature (° C)	Flowrate (μL/min)	Inlet concentration (M)	Observed reaction rate (kmol·kg ⁻¹ ·s ⁻¹)	C_{WP}
1	70	20	0.8	1.37E-06	0.74
2	70	20	1.6	2.36E-06	0.64
3	70	60	0.8	1.78E-06	1.03
4	70	60	1.6	2.92E-06	0.80
5	100	20	0.8	2.44E-06	0.77
6	100	20	1.6	4.63E-06	0.73
7	100	60	0.8	4.94E-06	1.55
8	100	60	1.6	8.97E-06	1.43

The calculation of the Weisz-Prater criterion, C_{WP} , yielded values greater than 1 for some of the experimental conditions, clearly indicating the presence of internal mass transfer resistances. The calculation was based on the assumption of a first order reaction. However, for more complex kinetic models, such as LHHW and ER, evaluating internal mass transfer resistances requires solving the diffusion-reaction equations within a single porous particle [397]. This requires that both the reaction rate constant and the adsorption equilibrium constants for all species participating in the reaction are known a priori. This is not always feasible for reactions where there is limited information on the available kinetic models. Therefore, the quantification of internal mass transfer resistances, through the calculation of the Thiele modulus, was not pursued here, due to constraints imposed both by the system and the catalyst. More specifically, the packing of smaller beads in a SPSR using vacuum was difficult to achieve, due to pressure drop across the bed. Furthermore, bead diameters smaller than 300 μm comprised less than 1% of the commercially available catalyst. As an alternative, internal mass transfer resistances were investigated experimentally by varying catalyst particle sizes. Catalyst particles with nominal diameters of 755 μm and 550 μm were tested, which swelled by 6%, resulting in effective diameters of 800 μm and 580 μm, respectively. A partial factorial design was employed, comprising four experiments (selected from those listed in Table 4-5) that were repeated twice. The reactors were loaded with equal catalyst mass but different particle sizes, and the resulting lactic acid (LA) conversion was compared in Figure 4-8. As shown in Figure 4-8, an average difference in conversion of 8% was observed for the experimental conditions studied between the bigger and smaller particles, suggesting the presence of internal mass transfer limitations.

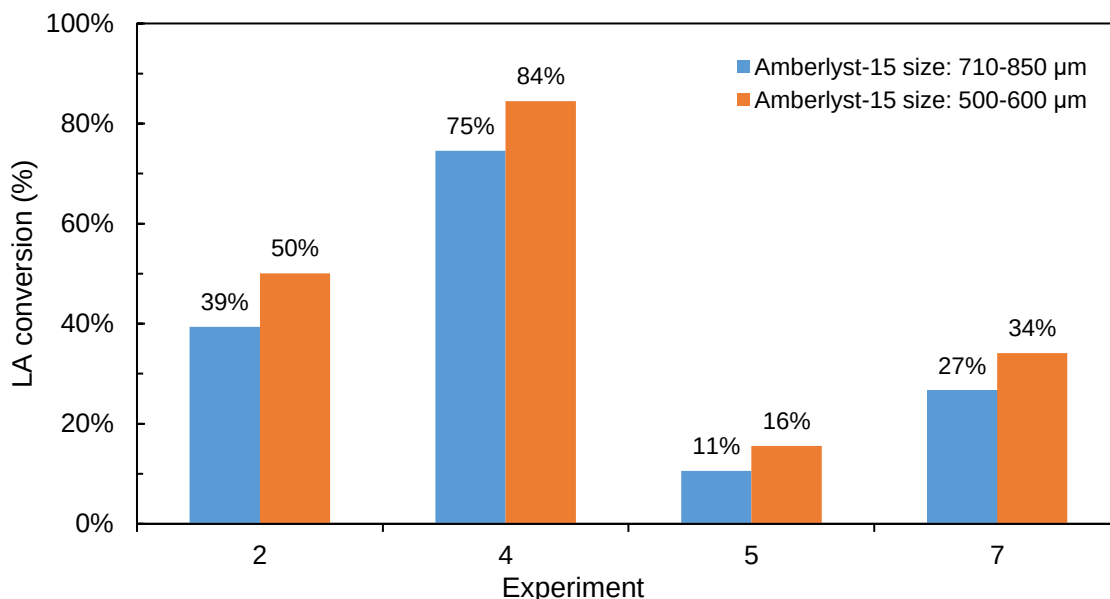


Figure 4-8. Conversion of LA using different Amberlyst-15 catalyst sizes. Each experiment corresponds to the experimental condition with the same number displayed in Table 4-5.

4.4.2. Influence of design space on model identification

Models with good fit but unidentifiable parameters are flexible enough to capture the complexity of the data, but their unidentifiable parameters can take any value without significantly affecting model predictions. These unidentifiable parameters could be a result of physical phenomena that are not captured by the dataset, e.g., because their effect is not measurable (such as low adsorption affinities) or due to a structural deficiency in the experimental design by overlapping and, thus, indistinguishable phenomena. The models proposed in Table 4-1, were therefore screened both for their adequacy to fit the experimental data as indicated by their χ^2 value and for their parameter identifiability, as indicated by the t-values.

Set 1 and 2 were compared to underline the influence of different operating conditions characterising the design space on model identification and parameter estimation. In each dataset, the measurement error was separately calculated. As an initial approach, adsorption equilibrium constants for the reaction components, K_i , were assumed temperature-independent, thus assigned a constant value, in the whole design space to decrease the complexity and computational effort required for the parameter estimation procedure. It is worth mentioning that the reaction rate constant, k , is always considered a function of temperature.

4.4.2.1. Model identification using experimental set 1

By applying the framework suggested in Figure 4-5, using the conditions of experimental Set 1 (without water in the feed), the results of model discrimination in terms of χ^2 statistics and practical identifiability, obtained after parameter estimation, are presented in Figure 4-9. LoF statistics are computed from Equation 4-11 and 95% reference value (representing the threshold value) is obtained from statistical tables for the relevant number of DoF. Identifiability was based on calculations of Equation 4-15, where models are classified as practically identifiable if all parameter estimates and all t-values are higher than 0.01, for a significance level of 5%. Compared to the t-test, this is a relaxed condition, and it is, therefore, complemented by the requirement of all absolute parameter cross correlation values, $C_{i,j}$, falling below 0.995.

As shown in Figure 4-9, only 7 out of the 28 models did not pass the model identification test, as their χ^2 value was higher than the χ^2 threshold, indicated by the dashed lines. Out of the 21 models left with χ^2 below the threshold, 6 contained identifiable parameters, indicated by green dots. The reason behind the unidentifiability of the models that passed the χ^2 test, when using experimental Set 1, can be attributed to the production of EL and water in identical concentrations, according to the reaction stoichiometry. This leads to high cross correlation of their relevant adsorption equilibrium coefficients, K_{EL} and K_W and high uncertainty in their estimation. LHHW models 16 and 17 and ER models 19 and 20, as well as 27 and 28 (red boxes in Figure 4-9), albeit identifiable, are characterised by pair-wise identical LoF values, which makes them pair-wise indistinguishable. Their indistinguishability is, also, related to the concentration of the products, as it can be seen from their denominators in the mathematical formulation in Table 4-1. The denominators only differ in the inclusion of either the adsorption coefficient of EL, K_{EL} , or water, K_W .

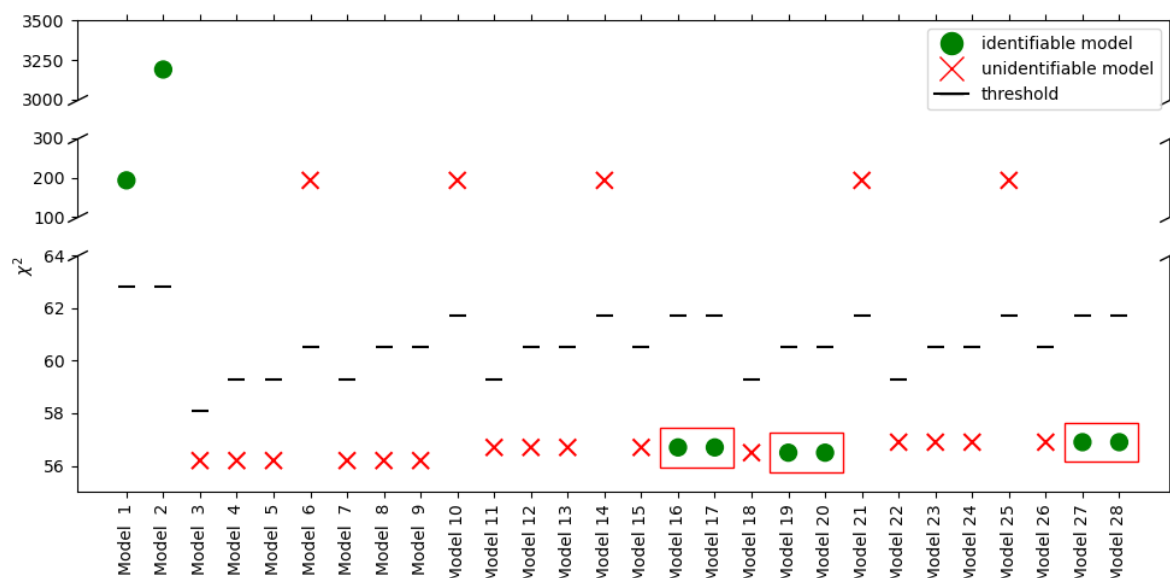


Figure 4-9. LoF metric, χ^2 , for the 28 kinetic models screened for Experimental Set 1. The red crosses indicate models with unidentifiable parameters, the green dots indicate models that are identifiable in the design space and the red boxes indicate pair-wise indistinguishability. The black dashed lines indicate the χ^2_{ref} (threshold) value.

4.4.2.2. Model identification using experimental set 2

The distinguishability challenges arisen from the correlation between the two reaction products when using Experimental Set 1, were overcome with the introduction of water at the inlet of the reactor to allow for differentiation of the outlet concentration for the products, introducing a new set of conditions, Experimental Set 2. The steps of the general procedure introduced in Section 4.3, were, once again followed. In Figure 4-10, the results of the model adequacy and identifiability are presented for all 28 models, are shown for Experimental Set 2. Removing the structural deficit associated with the reaction components' concentrations narrowed down the identifiable models to four, as it can be seen in Figure 4-10. However, the fitting of all the models in the design space explored was not statistically satisfactory, as underlined by the χ^2 test, indicating a poor fitting performance.

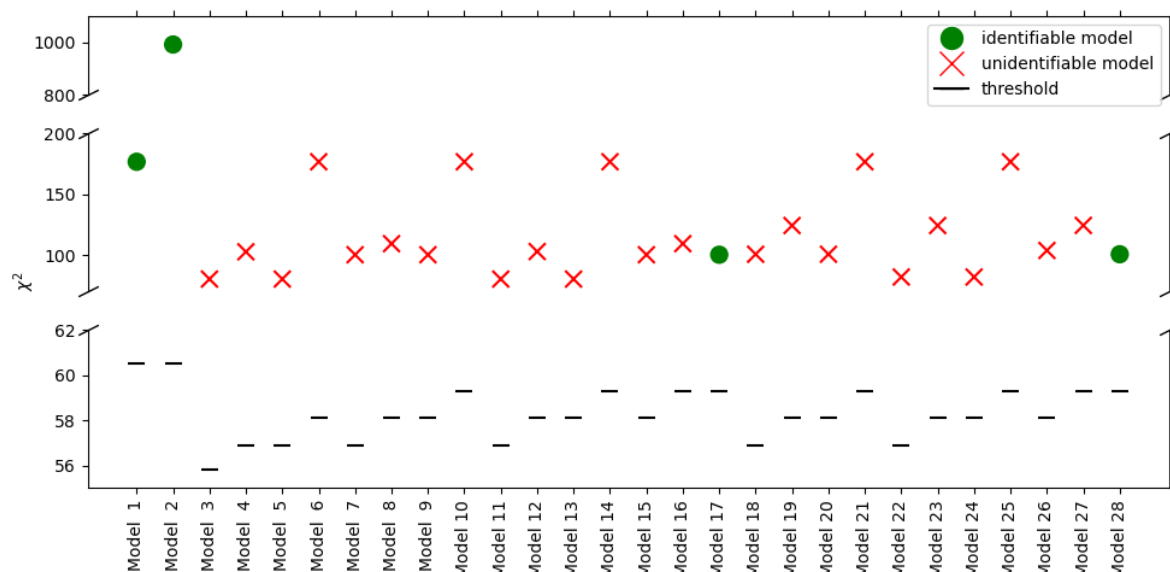


Figure 4-10. LoF metric, χ^2 , for the 28 kinetic models screened for Experimental Set 2. The red crosses indicate models with unidentifiable parameters, the green dots mark models that are identifiable in the design space. The black dashed lines indicate the χ^2_{ref} (threshold) value.

4.4.2.3. Model identification using both experimental sets

Given the results of Experimental Set 1 and 2 separately, none of the candidate models satisfied the criteria of structural identifiability and LoF simultaneously. For this reason, the use of both datasets was attempted. It must be stated that for each response variable the higher measurement variance from Experimental Set 1 or 2 was used as the estimated measurement error, Σ , of the blended dataset.

Figure 4-11 presents the results of model discrimination in terms of χ^2 statistics and practical identifiability when combining Experimental Set 1 and 2. The combination of the two sets, with Experimental Set 2 being an expansion of the design space of Experimental Set 1, resulted in a significantly higher number of identifiable models, out of which kinetic models 15, 16, 26 and 27 showed a clearly smaller χ^2 , close to the threshold value, as compared to others. These models were the ones brought forward to the next step for improvement of model fitting by introducing temperature dependent formulation of adsorption equilibrium constants. The models with χ^2 above but close to the threshold value imply adequate fitting, especially when compared to other candidate models, without fully describing the system's complexity.

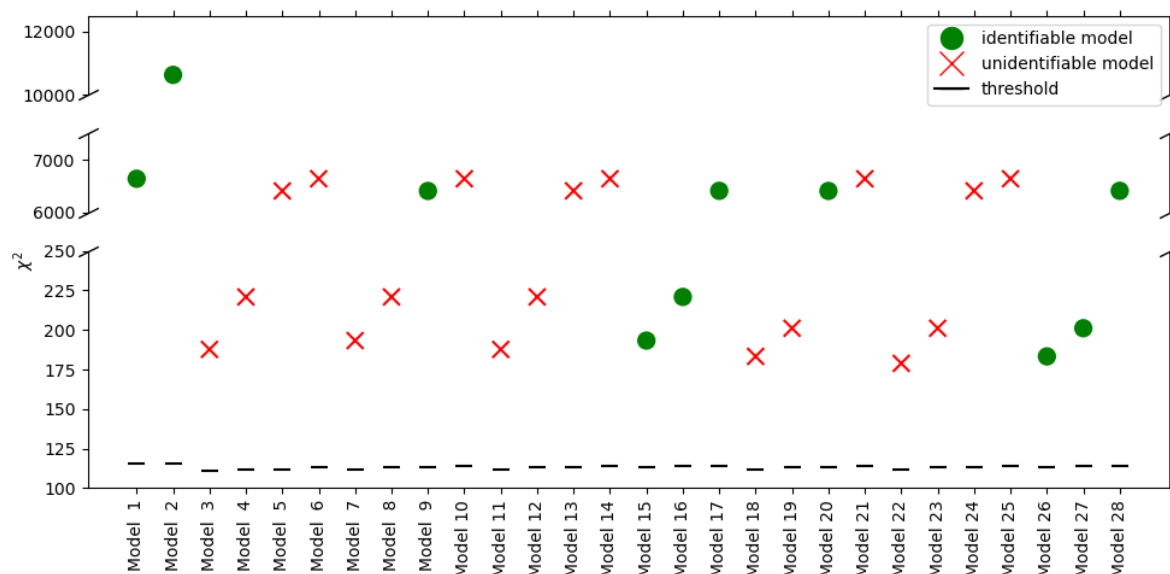


Figure 4-11. LoF metric, χ^2 , for the 28 kinetic models screened for combined Experimental Sets 1 and 2. The red crosses indicate models with unidentifiable parameters, the green dots mark models that are identifiable in the design space. The black dashed lines indicate the χ^2_{ref} (threshold) value.

4.4.3. Model identification using temperature dependency of equilibrium parameters

Having established the importance of combining the results of experiments conducted with (Experimental Set 2) and without the presence of water (Experimental Set 1) in the feed solution, in order to improve the fitting of the models successfully screened in Section 4.2, the incorporation of temperature in the calculation of adsorption equilibrium constants was taken into consideration, as described by Equations 4-3 to 4-6. In the kinetic models 15, 16, 26 and 27, the temperature dependency of the reaction rate constant and the adsorption equilibrium constants of water and EL was accounted for and the results of the combined data sets are shown in Figure 4-12. It is observed that the models' fitting to the experimental data is improved, by comparing the χ^2 values of Figure 4-12b, where the adsorption equilibrium for water and EL contains the temperature dependency of adsorption equilibrium for EL and water, and Figure 4-12c that includes the temperature dependency of adsorption equilibrium only for water, to the results of Figure 4-12a that were produced by assigning the adsorption equilibrium constants with a constant value, as performed in the initial approach. Furthermore, the contribution of the individual parameters on the χ^2 is different, with K_W dependency on temperature being stronger than K_{EL} , as seen by the negligible change in the χ^2 value when comparing the values of Figure 4-12b and Figure 4-12c.

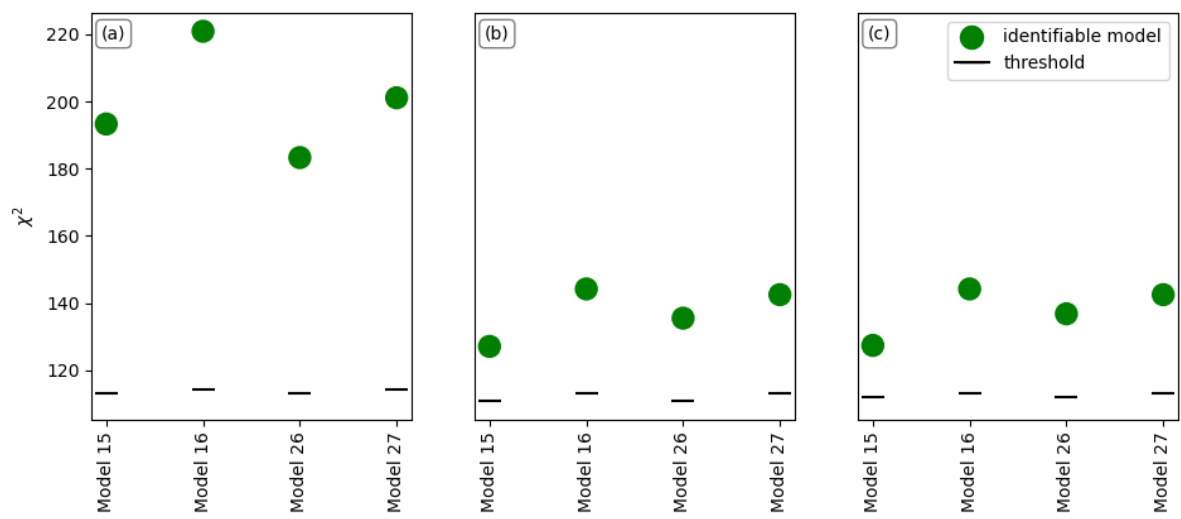


Figure 4-12. LoF metric, χ^2 , for the selected models from Section 4.4.2 for the combined experimental datasets (a) with constant adsorption equilibrium for water and EL, (b) including the temperature dependency of adsorption equilibrium for water and EL and (c) only including the temperature dependency of adsorption equilibrium for water but constant adsorption equilibrium for EL. The black dashed lines indicate the χ^2_{ref} (threshold) value.

Complementary to the evaluation of the fitting performance, the influence of temperature on the parameter estimation was investigated.

Table 4-6 presents the statistical precision of the parameter estimates for models 15, 16, 26 and 27, by assessing their 95% Confidence Intervals (Equation 4-16) and their Student's t-test values (Equation 4-17) for the two approaches followed: a) when the adsorption constants of water and EL were given a fixed value, hence the number of kinetic parameters to be estimated amounted to four and b) when they were varied with temperature resulting in models containing six kinetic parameters. A low Confidence Interval and a bigger t-test value than the reference t-value are indicative of satisfactory parameter estimation. As shown in Table 4-6, for the temperature-independent parameter estimates, the equilibrium adsorption constant of EL on Amberlyst-15, K_{EL} , was not estimated with good precision for model 26, a pattern that also emerged when incorporating temperature through the Van't Hoff equation for the same component, $K_{\text{P}_{\text{ads1,EL}}}$ and $K_{\text{P}_{\text{ads2,EL}}}$, for models 15 and 26. Therefore, based on the results of Figure 4-12, the expression of adsorption constants as a function of temperature improved the model adequacy, and models 16 and 27, which contained K_{W} as a temperature-dependent parameter, were deemed the most suitable, as they provided both the best fitting achievable (as shown in Figure 4-12) and reliable parameter estimates.

Table 4-6. Comparison of parameter estimation results for models 15, 16, 26 and 27 with and without considering temperature-dependent adsorption constants for water and EL for the combined Experimental Sets 1 and 2. The unidentifiable parameters are indicated in bold.

Parameter	Estimate	Confidence Interval [±]	t-value	Reference t-value
Temperature-independency				
Model 15				
KP ₁	14.80	0.05	319.21	1.99
KP ₂	5.54	0.12	45.27	
K _W	0.16	0.01	20.36	
K _{EL}	0.12	0.05	2.44	
Model 16				
KP ₁	14.90	0.02	801.69	1.99
KP ₂	5.34	0.09	58.16	
K _W	0.15	0.01	27.58	
Model 26				
KP ₁	14.76	0.06	262.85	1.99
KP ₂	5.53	0.12	45.71	
K _W	0.48	0.04	12.68	
K _{EL}	0.25	0.13	1.87	
Model 27				
KP ₁	14.86	0.02	697.24	1.99
KP ₂	5.38	0.09	57.34	
K _W	0.43	0.02	20.26	
Temperature dependency				
Model 15				
KP ₁₁	14.83	0.05	314.58	1.99
KP ₂	5.16	0.33	15.43	
K _W KP _{ads1,W}	1.81	0.05	36.44	
K _W KP _{ads2,W}	-1.07	0.36	2.99	
K _{EL} KP _{ads1,EL}	2.62	0.95	2.74	
K _{EL} KP _{ads2,EL}	1.68	6.9	0.24	
Model 16				
KP ₁	14.90	0.02	808.91	1.99
KP ₂	4.91	0.13	37.39	
K _W KP _{ads1,W}	1.86	0.04	49.28	
K _W KP _{ads2,W}	-1.21	0.27	4.44	
Model 26				

KP ₁		14.81	0.05	274.36	
KP ₂		5.21	0.38	13.74	
K _W	KP _{ads1,W}	0.76	0.08	10.07	1.99
	KP _{ads2,W}	-1.11	0.53	2.08	
K _{EL}	KP _{ads1,EL}	3.61	29.36	0.12	
	KP _{ads2,EL}	13.19	216.91	0.06	
Model 27					
KP ₁		14.85	0.02	697.54	
KP ₂		4.91	0.15	32.44	
K _W	KP _{ads1,W}	0.80	0.05	15.60	1.99
	KP _{ads2,W}	-1.42	0.37	3.83	

The final rate expressions for the LHHW (model 16) and ER (model 27) mechanisms are shown in Equations 4-26 and 4-27, respectively. In Table 4-7, the relevant parameters and their units are presented. The factorial design-generated experimental data of the combination of Experimental Sets 1 and 2, were compared to the predicted data of models 16 and 27. The adequacy of the models proposed is demonstrated graphically in the parity plots of Figure 4-13, where the model predictions, both for the concentration of LA (Figure 4-13a) and for the concentration of EL (Figure 4-13b) fell around the interval of the maximum error, calculated as 2 times the experimental standard deviation. Although there were not any obvious differences in the performance of models, as observed in Figure 4-13, a good agreement of both model predictions with the experimental data was established.

$$r'_{LA} = \frac{4.90 \cdot e^{\left(-\frac{49100}{RT}\right)} C_{LA} C_{EtOH}}{\left(1 + 0.16 \cdot e^{\frac{12100}{RT}} C_W\right)^2} \quad (4-18)$$

$$r'_{LA} = \frac{5.15 \cdot e^{\left(-\frac{49100}{RT}\right)} C_{LA} C_{EtOH}}{\left(1 + 0.45 \cdot e^{\frac{14200}{RT}} C_W\right)} \quad (4-27)$$

Table 4-7. Estimated parameters for the LHHW (model 16) and ER (model 27) mechanisms.

	Model 16	Model 27
A ($L^2 g^{-1} s^{-1} mol^{-1}$)	4.90	5.15
E_{α} ($J mol^{-1}$)	49100	49100
$K_{W,ref}$ ($L mol^{-1}$)	0.16	0.45
ΔH_W ($J mol^{-1}$)	-12100	-14200

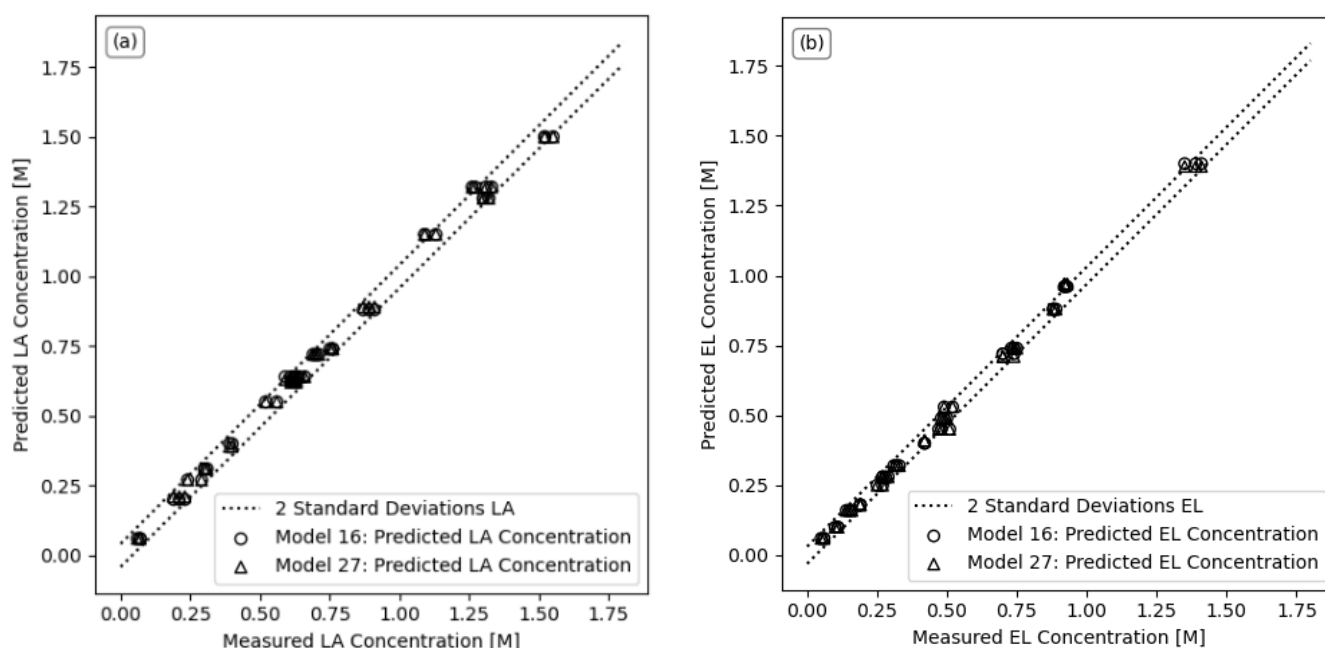


Figure 4-13. Reactor outlet concentration parity plots of the selected kinetic models (Model 16 and Model 27) for (a) LA and (b) EL, from the combination of experimental Set 1 and 2. The dashed lines represent the two-standard deviation limits.

In this work, the apparent activation energy of the levulinic acid esterification with ethanol, E_{α} was 49.4 kJ/mol for both reaction kinetic models proposed, and the lumped kinetic rate constant, k , at the mean experimental temperature (reference temperature) of 85 °C was estimated equal to $3.056 \cdot 10^{-7} L^2 g^{-1} s^{-1} mol^{-1}$ for LHHW and $3.212 \cdot 10^{-7} L^2 g^{-1} s^{-1} mol^{-1}$ for ER respectively. Comparing with existing literature, Russo et al. [366] reported an activation energy of 45.2 kJ/mol for Amberlyst-15 beads of 300 μm and 49.4 kJ/mol for beads of 600 μm , assuming that the levulinic acid esterification with ethanol was pseudohomogeneous first order with respect to both reactants. Sharma et al. [398] reported an activation energy of 46.4 kJ/mol in the presence of Amberlyst-15 500 μm particles for the esterification of pentanoic acid with 1-propanol that followed ER kinetics, with a kinetic rate constant equal to $2.325 \cdot 10^{-7} L^2 g^{-1} s^{-1} mol^{-1}$ at 85 °C.

The enthalpy of adsorption for water in the LHHW proposed mechanism was estimated equal to $\Delta H_W = -12.1$ kJ/mol and $\Delta H_W = -14.2$ kJ/mol for ER, which is indicative of components adsorbed physically on the surface of the ion-exchange resin [399], with the enthalpy of adsorption being higher than the one presented for esterification reactions on the same catalyst, as presented in the work of Lux et al. [383], where $\Delta H_W = -4.78$ kJ/mol. At the reference temperature of 85 °C, the value of K_W ($K_{W,ref}$) was calculated equal to 0.16 L/mol for LHHW and 0.45 L/mol for the ER model. The values of the adsorption equilibrium constants estimated cannot be directly compared with reported values from Lux et al [383], as they derive from the concentrations of components and not thermodynamic activities, and the reaction, as well as the range of the temperatures investigated, are completely different. Comparing the estimated adsorption equilibrium constants with the ones provided by Sharma et al. [398] for the esterification of pentanoic acid with 1-propanol, K_W is approximately 0.50 L/mol at 85 °C and 1.76 L/mol for the synthesis of 1-propanonanoate at the same temperature [400]. It is apparent that the reported values for similar esterification systems are in the same range as the ones reported in this work.

Prior studies in the literature have included adsorption experiments on Amberlyst-15 for other liquid-phase esterification reactions, with the heterogeneous methyl acetate synthesis being an extensively examined reaction. Song et al. [401] performed nonreactive binary adsorption experiments for the esterification of acetic acid with methanol at 45 °C, and reported that water adsorption equilibrium constant is twice as high as this of methanol, followed by acetic acid and methyl acetate. Pöpken et al. [402] compared the experimental data fitting on a pseudohomogeneous and an adsorption-based heterogeneous LHHW model. The adsorption experiments, conducted at 25 °C, revealed that the reaction's components adsorb similarly on Amberlyst-15, as shown by the magnitude of their respective equilibrium adsorption constants. Sharma et al. reported the kinetics of an extensive range of liquid phase esterification reactions on Amberlyst-15 [375, 398, 400, 403, 404], all of which followed an ER mechanism with the adsorption of water and the relative alcohol dominating over the one of the acid and the produced ester. Based on the final reaction rate expressions suitable to fit the experimental data in this work (Equations 4-18 and 4-19), water adsorption on the Amberlyst-15 surface is stronger than the rest of the reaction components, including ethanol that is the solvent. This is consistent with the above literature findings and aligns with the hypothesis that the polarity of the reaction components plays a pivotal role in the observed phenomena [383]. Notably, water, being the most polar component, manifests the most pronounced inhibitory effect. To ascertain the precise hierarchy of polarity and, subsequently, the magnitude of adsorption of levulinic acid and ethyl levulinate on Amberlyst-15, it is imperative that further investigation is conducted (e.g. use of FTIR microspectroscopy on Amberlyst-15 beads for different

experimental conditions) to yield comprehensive insights into the complex interactions of the resin with the keto-acid and its derivative respectively.

4.5. Conclusions

The esterification of levulinic acid with ethanol in the presence of Amberlyst-15 was carried out in a continuous Single Pellet String Reactor, as part of an automated platform controlled by LabVIEW. Due to the macroreticular structure of the catalyst and the commercially available sizes, internal mass transfer resistances could not be excluded and therefore, the kinetic models reported reflect apparent kinetics. A systematic screening of kinetic models was performed, including model adequacy and estimation of identifiable parameters, of both simple and of increased complexity models (i.e., reaction rate expressions with high number of parameters). The combination of two experimental data sets (with and without the introduction water in the feed), as well as the integration of temperature dependent equilibrium adsorption constants, shed light into the effect of choosing the right design space and how fitting of seemingly inadequate models can be improved. Apparent kinetics and thermodynamic parameters were precisely estimated. A Langmuir-Hinshelwood-Hougen-Watson model and an Eley-Rideal model, including a temperature-dependent term for the adsorption equilibrium of water were found to be the most appropriate kinetic models for the production of ethyl levulinate from levulinic acid in the investigated design space. In both proposed models, it was observed that water exhibited a strong tendency to bind to the catalytic sites, thereby inhibiting the reaction. Due to the similarity between the two final reaction rate expressions, it was not possible to discriminate further. Future work will target issues related with the distinguishability of the competing models by using Model Based Design of Experiments techniques for model discrimination and parameter estimation with the highest precision.

Chapter 5. Design and hydrodynamic characterisation of a miniaturised CSTR for kinetic studies using inline Raman spectroscopy

5.1. Introduction

Delivering high quality products at a reduced cost via greener processes necessitates the extraction of quantitative chemical synthesis information. This involves the development of a precise reaction kinetic model that serves as a cornerstone for process design and optimisation [405]. Although, the application of micro and milli-scale reactors for developing kinetic models in continuous flow processes has been extensively demonstrated [20, 46, 51, 70, 153-157, 187, 355, 406-408] coupling platforms with in-situ and operando spectroscopic techniques marks a paradigm shift in real-time reaction monitoring. This approach enables rapid qualitative and quantitative analysis of the various reaction species, and stands as an equally reliable alternative to well-established online analytical techniques such as HPLC or GC, which are typically associated with time-consuming procedures [176].

Raman spectroscopy allows for fast, contact-free, non-destructive sampling with high chemical specificity and can be readily used in organic and aqueous systems, without water interference [220]. Although traditionally associated with qualitative analysis, Raman spectroscopy proves effective in quantitative applications by leveraging the linear proportionality between the intensity of an analyte band and its concentration [409]. The recent advances in Raman process spectrometers, equipped with flow cells and contactless probes, enhance their seamless integration into flow processes. This progress diminishes the reliance on Raman microscopes, which, despite their improved spatial resolution, can be prohibitively expensive [410]. Moreover, the contact-free features of benchtop Raman spectrometers mitigates the need for immersing probes in corrosive or reactive media [227], thereby minimising factors that might disrupt accurate quantification, such as deposition of reaction products on collection optics [411]. Despite the advantages of Raman spectroscopy, its implementation for quantification faces challenges like fluorescence and sample turbidity. Strategies that involve opting for a long excitation wavelength, typically 785 nm that doesn't obfuscate the features of interest [412], and advanced data processing techniques to eliminate fluorescence [413] and correct the turbidity interference [414] can mitigate these effects.

Schwolow et al. [176] showcased the application of a contactless Raman probe to determine reaction kinetics of the synthesis of 3-Piperidino propionic acid ethyl ester, under steady and transient conditions, in an aluminium plate microreactor covered with fused-quartz. Cao et al. [415] introduced a microreactor system featuring four micro-packed beds, enabling the study of the multiphase (gas-liquid-solid) oxidation of benzyl alcohol. This was accomplished while employing a portable Raman spectrometer. Notably, both these studies shared two common aspects: the integration of operando Raman spectroscopy for kinetic studies and the intricate

channel geometries of the microfluidic chip reactors used, enabling the switch between multiple measurement locations, a feature particularly well-suited for rapid reactions. However, for reactions requiring extended residence times, adjustments to the microchannel lengths would be necessary. These modifications could result in elevated pressure drops and prolonged time and material consumption before achieving a steady-state condition [416, 417]. To address this challenge, Klement et al. [417] presented a novel concept involving a sandwich minichannel reactor for oscillating droplets that allowed for the measurement of individual droplets within a PTFE channel using Raman spectroscopy. The same group of authors streamlined the reactor configuration and successfully applied Raman spectroscopy to elucidate the kinetics of acrylic acid polymerisation in slug flow [418]. Moreover, Schulz et al. [68], utilising the same reactor setup, reported their findings on the kinetics of an imine synthesis, employing Raman spectroscopy for quantification and coupling it with chemometrics.

Another recently developed technology that can circumvent the above challenges is miniaturised Continuous Stirred Tank Reactors (m-CSTRs). With volumes of a few mL, m-CSTRs benefit from the properties of microreactors [419], while also allowing for good mixing based on active stirring [420, 421], thus offering unique advantages for solid-producing reactions [76, 78, 422, 423], multiphasic flow chemistry [424] and investigation of slower reaction kinetics [75]. Although, the development of the m-CSTR technology holds promise for both research and production for increasing yield and overcoming mass-transfer limitations, there are no reports on their employment for acquiring reaction kinetics in continuous flow with the aid of inline spectroscopy, to the best of the author's knowledge.

A noteworthy aspect of employing a m-CSTR for kinetics is the reactor's versatility to operate both in batch and continuous mode, with minimal modifications. Guan et al. demonstrated this adaptability in the Pd/C-catalysed hydrogenation of nitrobenzene, benefitting from identical mass transfer coefficients in both batch and continuous flow settings [425]. Another inherent benefit of using this type of reactor lies in the ease of window replacement, allowing for direct coupling with non-invasive spectroscopic techniques like Raman (using quartz windows) or transmittance IR (with CaF_2 windows). Although m-CSTRs do not provide insights into intermediate reaction steps since they operate at outlet conditions, the integration of a flow cell immediately after the reactor is easier. However, when operating in a cascade set-up that permits a narrower Residence Time Distribution (RTD) profile [426], investigating kinetics in each CSTR would require multiple spectroscopic flow cells and additional tubing. This can give rise to susceptibility to clogging, particularly in reactions that generate solid precipitates. In contrast, the use of a non-invasive Raman probe with an open beam, mounted on a

motorised positioning stage or on inexpensive 3D printed Raman holders in each unit, offers the advantage of an immediate system response where mixing happens.

To bridge this existing gap in literature, our work introduces a temperature controlled miniaturised CSTR, equipped with an inline Raman spectrometer probe to obtain kinetic data. The m-CSTR's mixing characteristics are thoroughly investigated through both experimental and computational approaches and its efficacy to produce fast reaction kinetics data is demonstrated for an imine synthesis reaction in an automated experimental platform.

5.2. Materials and methods

5.2.1. Reactor design and fabrication

Since the main goal of this work was to develop a reactor that can be readily coupled with Raman spectroscopy for reaction kinetics and can operate in a wide range of temperatures (sub-ambient to high temperatures) and pressures of up to a few bars, the design and materials of the m-CSTR were carefully evaluated. The m-CSTR consists of the following five main components:

1. Reactor chamber: Constructed from 316 stainless steel, the cylindrical chamber has an internal diameter of 15 mm and a depth of 15 mm, resulting in a total volume of 2.65 mL.
2. Optical window: A quartz optical grade window (Knight Optical) with a diameter of 15 mm and a thickness of 2 mm is placed on top of the reactor chamber. This window allows for inline Raman spectroscopy to be performed.
3. Reactor lid: A 316 stainless steel lid seals the reactor chamber together with the optical-grade window, ensuring a secure and leak-proof environment.
4. Cooling/heating jacket: The jacket, also made of 316 stainless steel, has a squared main body (90 mm x 90 mm x 24.65 mm) with an inner protruding fin to enhance the recirculation of the heating fluid
5. Reactor cover: A 316 stainless steel reactor cover is used to minimise heat loss due to convection with the surrounding environment, ensuring stable temperature conditions within the reactor.

Two 2 mm I.D. holes are drilled at a 90° angle to each other on the side walls in close proximity to the bottom of the reactor chamber, designed for the introduction of the reactants. A 2 mm I.D. hole, used as the outlet, is drilled on the side wall, 4 mm below the top of the reactor chamber, to minimise short-circuiting of the reacting mixture. A custom-made impeller with dimensions of 8 mm in height and 13 mm in diameter and a total volume of 0.24 mL is designed

and fabricated from PTFE. The impeller features a pocket for fitting a high-pull rare earth magnet and machined edges with 1.5 mm slots, allowing coupling with an external magnetic stirring unit to control the impeller's rotational speed. All the reactor components, including the impeller, were machined using CNC milling (Haas TM1P Vertical Machining Centre). The whole unit has the capability to withstand harsh chemical environments and the integration of a heating jacket allows conducting reactions at the desired temperature by connecting it with a circulating bath. The flexibility in the choice and easy replacement of the window renders the reactor suitable not only for Raman spectroscopy but also for other spectroscopic techniques (with necessary adjustments). A custom-made holder to house the Raman probe for reproducible sampling was 3D-printed of high-temperature resin (Appendix C, Section C1).

Figure 5-1 shows the CAD design and the assembled reactor and Figure 5-2 illustrates the different reactor components (Further details are provided in Appendix C, Section C1).

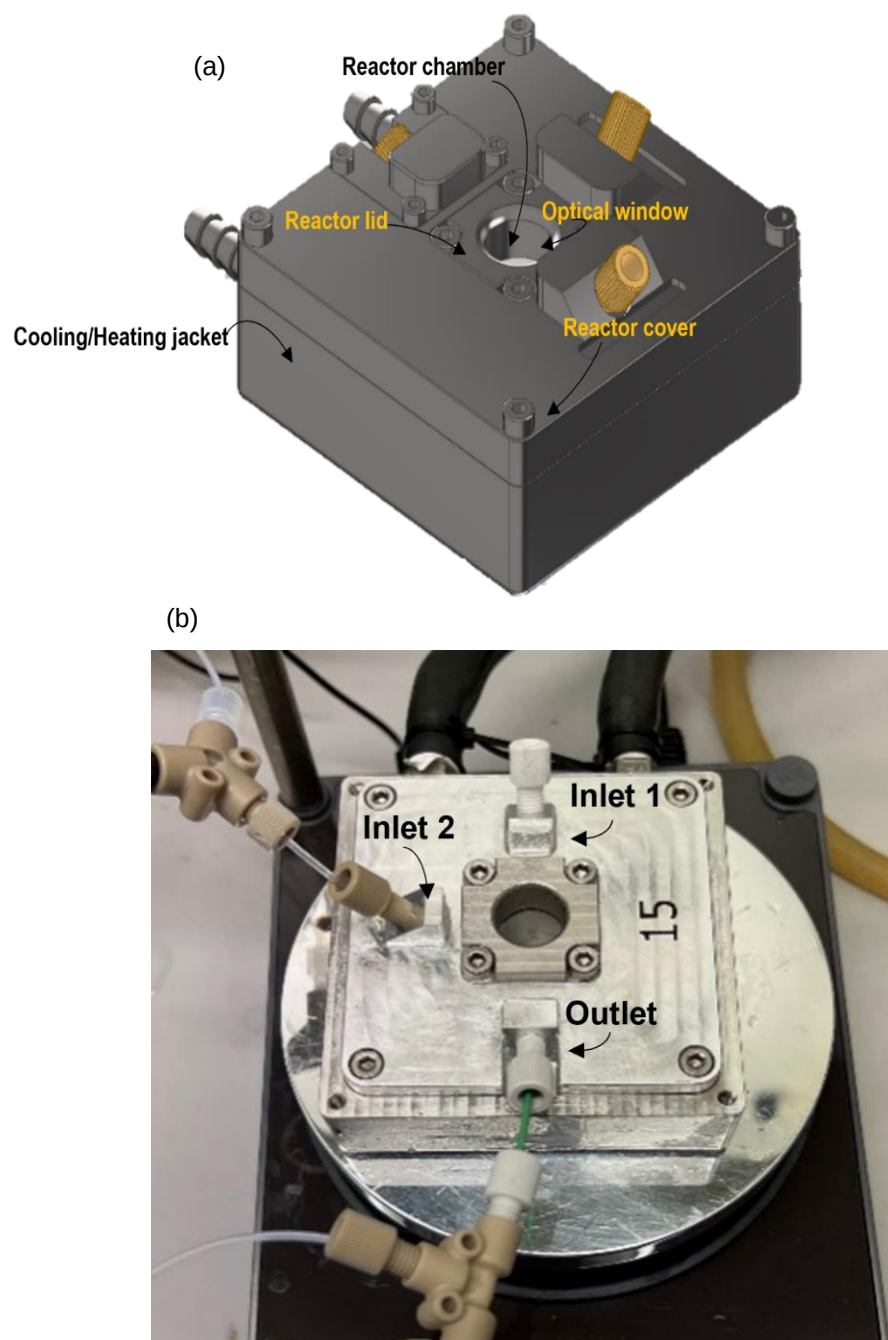


Figure 5-1. (a) CAD design and (b) picture of assembled m-CSTR

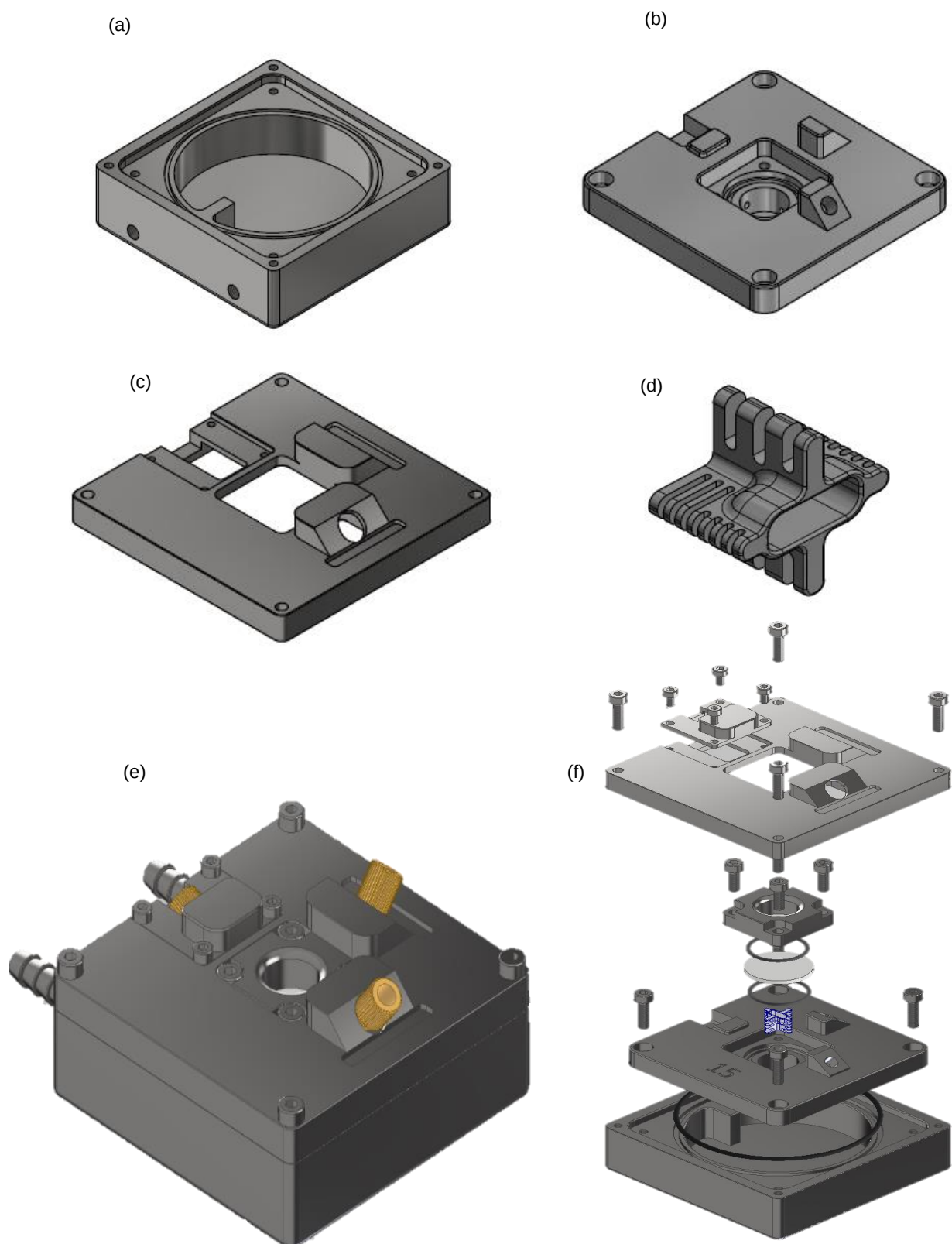


Figure 5-2. m-CSTR components (a) heat-exchange jacket, (b) reactor chamber with inlet and outlet ports, (c) the reactor cover, (d) a custom-made (slotted) impeller, (e) full reactor assembly and (f) exploded reactor assembly.

5.2.2. Mixing characterisation

The microfabrication of reactors and their potential for industrial-scale applications have necessitated the development of complementary components, including micromixers [427, 428]. Mixing is characterised by macromixing and micromixing, with the effectiveness of one not necessarily guaranteeing the effectiveness of the other. In stirred tanks, micromixing prevails near the impeller, while the broader surrounding region is predominantly associated with macromixing [429]. RTD studies represent the distribution of time intervals that elements of fluid remain inside the reactor and reflect the macromixing characteristics and flow patterns [90]. Micromixing performance, usually characterised by competitive chemical reactions, describes the extent of mixing on the molecular scale [112]. In this work, two different impellers were experimentally evaluated for efficient micro-mixing of the miniaturised CSTR: a magnetic PTFE cross-shaped stirring bar (VWR, UK) with height of 5 mm and diameter of 10 mm and the custom-made PTFE impeller, which was described in Section 5.1. As an additional feature, the hydrodynamic behaviour in the miniaturised stirred tank was computationally examined for the same range of flowrates and stirring speeds as the experimental conditions.

5.2.2.1. Residence time distribution characterisation

To characterise the macromixing behaviour of the miniaturised CSTR and quantify deviations from ideal behaviour, such as dead volume and bypass, the RTD of the CSTR unit was obtained using the step injection method, as shown in Figure 5-3a. The carrier phase was deionized (DI) water, and the tracer was a solution of methylene blue (0.0085 mg/ml, Basic Blue 3, Sigma Aldrich) with a maximum UV-Vis absorbance peak of ~ 0.8 at 652 nm. Prior to the RTD study, the concentration of methylene blue was correlated with its UV-Vis peak absorbance at the same wavelength revealing a linear relation between concentration and absorbance in the investigated region. Since the reactor has two available inlets, experiments were conducted using one and both inlets. For the single inlet RTD experiments, a syringe pump (Hamilton) was used for pumping the blue dye and DI water through a six-way valve (IDEX Health & Science LLC, MXP7900-000) in one of the inlets, whilst keeping the other one blocked, to achieve a step tracer change. In the case of two inlets, an additional syringe pump was employed that continuously pumped DI water in the second inlet. The reactor was stirred by adjusting the rotational speed in a digital hotplate stirrer (Stuart, Cole-Palmer LLC). Flowrates similar to the reaction kinetics experiments were used ranging from 0.25 to 4 mL/min and stirring speeds of 250, 500 and 1000 rpm were investigated. The tracer concentration was monitored at the reactor outlet using UV-Vis spectroscopy. A custom, no-contact flow cell was employed [430], where a transparent FEP outlet tube (1 mm optical path length, matching the

inner diameter of the tube) was positioned perpendicular to the optical fibres, enabling direct measurement of the optical absorbance at the reactor's outlet. The absorbance was measured using a UV-Vis spectrometer (Ocean Optics, USB2000+) with a deuterium-halogen light source (Ocean Optics). The DI water background was subtracted before the experiment. The integration time was set to 30 ms and scans were taken approximately every 1 s. Each experiment was repeated at least twice, interchanging the reactants between the inlets to ensure that the results are independent of the inlet position.

A short section of tubing was used to connect the inlet of the reactor to the six-way switching valve and the outlet of the reactor to the UV detection point, respectively. Despite its relatively short length, the outlet concentration profile of the system was a convolution of the RTD of the reactor and the connecting tubing. Since there was interest only in the m-CSTR's RTD, an additional RTD experiment was performed connecting the inlet and outlet capillary sections directly to evaluate their contribution to the system's output. Data from the reactor outlet post-step injection were collected, including both the system output and the tubing output, and processed using a dual-filtering approach combining a moving average and Savitzky-Golay filters to reduce noise [431]. The moving average filter, constrained within a narrow window of approximately 30 data points (equivalent to around 1 second of experimental time), facilitated refinement of the fitting process for the subsequent Savitzky-Golay filter. After smoothing, the absorbance data were normalised using the maximum experimental absorbance value. RTD curves ($E(t)$) for both the system and tubing were derived by differentiating the normalised absorbance data using MATLAB's 'gradient' function. Recognising that convolution in the time domain corresponds to multiplication in the frequency domain, the discrete (Fast) Fourier transform (FFT) was applied to both the system and tubing RTD curves. By dividing the FFT of the system RTD by that of the tubing, the deconvoluted RTD of the reactor was effectively generated, followed by an inverse FFT via MATLAB's 'ifft' function to transform the result back into the time domain. Due to noise amplification in the differentiation process, a secondary smoothing using larger Savitzky-Golay windows tailored to the volume of data was applied, particularly at lower flow rates. For instance, at the lowest flow rate explored (0.25 mL/min), a window of 501 data points for Savitzky-Golay filtering was chosen. Despite the seemingly extensive window size (equivalent to approximately 17 seconds of experimental time), it is noteworthy that the absorbance changes were gradual, taking over 15 seconds to approach a plateau, with no abrupt variations observed. Thus, the adoption of larger windows was warranted to ensure robust noise reduction. The $E(t)$ curves were then transformed into dimensionless $E(\theta)$, by multiplying with the reactor's residence time, calculated using the trapezoid rule for integration via MATLAB's 'trapz' function. This enabled comparison with the

ideal CSTR model $E_{\theta, \text{model}}$ (Equation 5-1) to quantify derivations from ideal behaviour by evaluating the fitting quality between the experimental RTD curve and the model RTD curve through the calculation of the Root Mean Square Error, RMSE_{RTD} (Equation 5-2). It is considered that the fitting is acceptable when the difference between the RTD curve fit and the experimental data is below 10%.

$$E_{\theta, \text{model}} = e^{-\theta} \quad (5-1)$$

$$\text{RMSE}_{\text{RTD}} = \sqrt{\frac{\sum_{\theta=0}^{\theta=\theta_{\text{max}}} (E_{\theta, \text{model}}(\theta) - E_{\theta}(\theta))^2}{\sum_{\theta=0}^{\theta=\theta_{\text{max}}} E_{\theta, \text{model}}(\theta)^2}} \quad (5-2)$$

where, $\theta = t/\tau$ is the normalised mean residence time, t is the absolute time, $\tau = Q/V_R$ is the space time of the reactor, Q is the volumetric flow rate entering the reactor and V_R is the total free volume of the reactor (after subtracting the volume of the impeller).

The dimensionless number, Re_M (Equation 5-3) that represents the stirring Reynolds number is used to describe the hydrodynamic properties of the system.

$$\text{Re}_M = \frac{\rho N D_s^2}{\mu_L} \quad (5-3)$$

Where, ρ is the solution density (kg/m^3), μ_L is the solution dynamic viscosity ($\text{Pa}\cdot\text{s}$), D_s is the diameter of the impeller (m) and N is the rotational speed of the impeller (s^{-1}).

5.2.2.2. Micromixing analysis

To quantify the performance efficiency of micromixing, the Villermoux-Dushman rapid parallel competition reaction system was used, as introduced in Section 2.1.3.2 of this thesis. This particular reaction system involves the addition of sulfuric acid (3 M stock solution, Alfar Aesar) to a buffer solution containing a mixture of orthoboric acid (99.5% Sigma-Aldrich), sodium hydroxide (2 M, Sigma-Aldrich), potassium iodide (99%, Sigma-Aldrich), and potassium iodate (98% Sigma-Aldrich) ions.

For the mixing experiments, the concentrations proposed by Commenge and Falk [112] that can be found in Table 5-1, were used. The final triiodide concentration was obtained using an extinction coefficient of $23,209 \text{ L mol}^{-1} \text{ cm}^{-1}$ [130]. To account for the effect of potential faults in the fabrication procedure of the m-CSTR, the experiments were repeated by switching the inlets, where no difference was observed on the obtained results. Experiments were repeated three times for each mixing configuration.

Similar to the experimental rig used for the macromixing experiments (Figure 5-3a), in Figure 5-3b, the experimental set up for the Villiermaux-Dushman reaction is presented. The prepared acid and buffer solutions were loaded separately in 100 mL syringes (SGE) and were pumped simultaneously by the same syringe pump (Hamilton). The reactor was stirred by adjusting the rotational speed in a digital hotplate stirrer (Stuart, Cole-Palmer LLC). Flowrates similar to the RTD and reaction kinetic experiments were used ranging from 0.5 to 4 mL/min and stirring speeds of 250, 500, 750 and 1000 rpm were investigated. The outlet of the m-CSTR was connected to the UV-vis analysis set-up by 1 m long PFA tubing (delay loop) to make sure the reactions are completed and equilibrated. To ensure this length of the tubing was sufficient, the experiment was tested with 6m long tubing, which resulted in the same absorbance of triiodide. The tracer concentration was monitored at 353 nm, using the same UV-Vis system, as in the RTD experiments (Section 5.2.1).

Table 5-1. Initial concentrations of reagents used to characterise micromixing in the miniaturised CSTR, working with two equal inlet flowrates, as proposed by Commenge and Falk [112].

Reagents	Initial concentrations (M)
H ₂ SO ₄	0.02
KI	0.032
KIO ₃	0.006
NaOH	0.09
H ₃ BO ₃	0.09

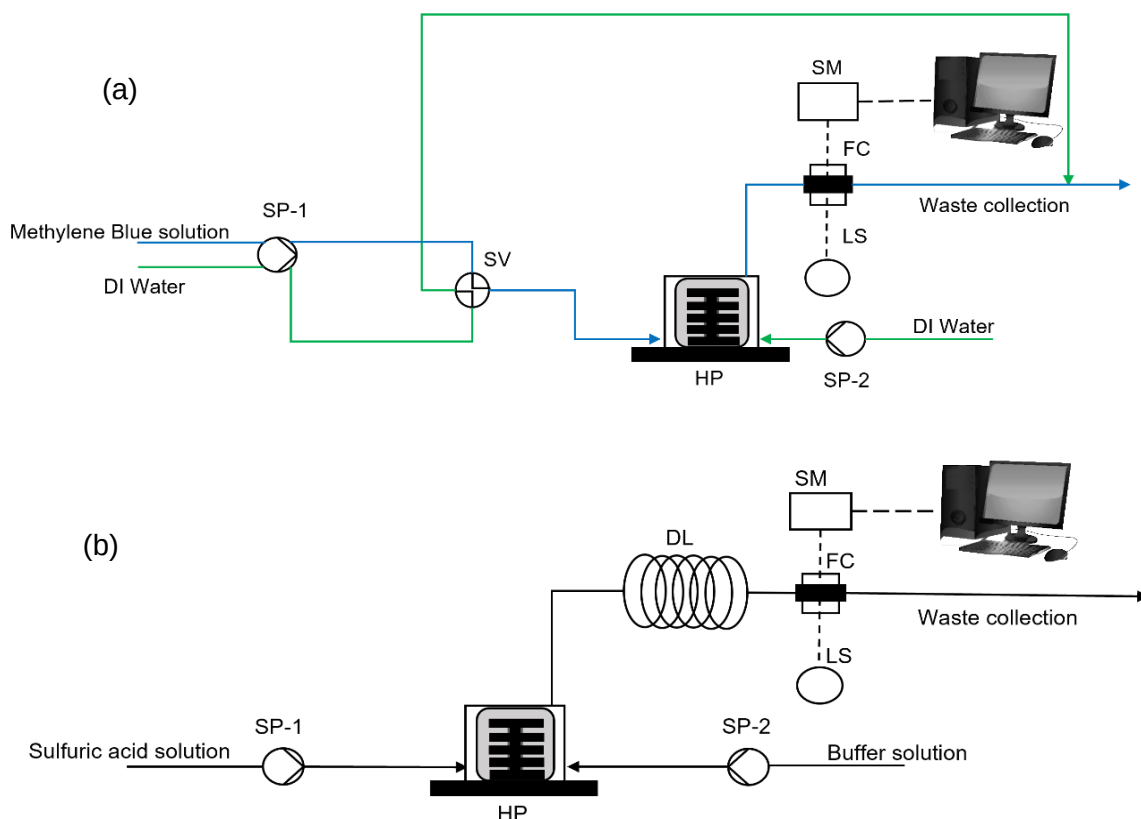


Figure 5-3. (a) Experimental set-up for the Residence Time Distribution (RTD) studies (green lines indicate the DI water flow and blue lines indicate the blue dye flow) and (b) Villiermaux-Dushman experimental rig. SP: syringe pump, SV: switch valve, SM: spectrometer, FC: flowcell, LS: light source, DL: delay loop, HP: stirrer-hotplate.

5.2.2.3. Modelling of hydrodynamics

Although there is extensive literature on modelling the mixing conditions in stirred tank vessels [132, 432-436], the direct transferability of the physical phenomena to a small-scale system is not straightforward. One of the main differences lies upon the dimensions of the impeller in the present system, which are similar to these of the reactor chamber, therefore, sweeping the whole volume of the bulk fluid. To shed light into the hydrodynamics in a miniaturised CSTR, Computational Fluid Dynamics (CFD) modelling was conducted using COMSOL

Multiphysics® v. 6.1 on a DELL OptiPlex 7060 Windows operated PC with Intel Core i7-8700 CPU and 16 GB of RAM.

The geometry of the modelled CSTR was an exact replicate of the experimental device, as shown in Figure 5-4. The computational domain was divided in two to represent the circulating fluid; an inner rotating cylindrical volume that encloses the impeller (denoted as Domain 2 in Figure 5-4) and an outer stationary volume that occupies the remainder of the vessel (denoted as Domain 1 in Figure 5-4), including the two inlets and the outlet. To reduce the computational cost of performing unsteady simulations in the stirred system, the steady-state Multiple Frame of Reference technique of the frozen rotor was used [437]. The impeller was elevated by 200 μm from the bottom surface of the tank to facilitate meshing of good quality.

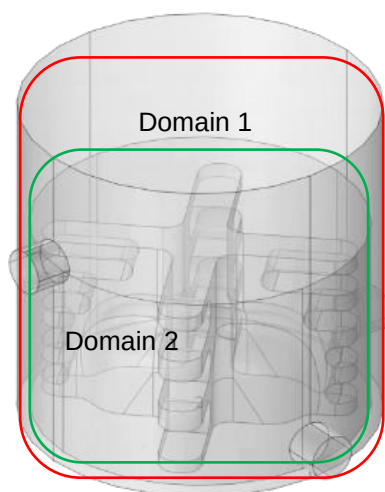


Figure 5-4. Replicate of the miniaturised CSTR COMSOL Multiphysics® v. 6.1. Domain 1 (in red) includes the outer stationary volume that occupies the vessel volume, excluding the impeller and Domain 2 (in green) represents the inner rotating cylindrical volume that encloses the impeller.

Water at 20 °C was chosen as the working fluid for all simulations. In Table 5-2, the Reynolds number for the stirred tank, as calculated in Equation 5-4, is reported. For all the stirring speeds studied, Re_M was higher than 100, which is the upper limit for laminar flow but less than 20000, where the flow can be considered fully turbulent [438]. Therefore, it was expected that the flow field would display areas with high turbulence (close to the impeller) and areas where laminar flow dominates (close to the vessel walls). For modelling the complex hydrodynamics of the miniaturised tank, the RANS realisable k - ϵ turbulence model was employed [439-441]. The realisable k - ϵ turbulence model involves solving the conservation equations for the turbulent kinetic energy, k , (Equation 5-10) and the turbulent energy dissipation rate, ϵ , (Equation 5-11) along with the Navier-Stokes equation (Equation 5-8) and continuity equation (Equation 5-9) in steady-state conditions. The flow was considered incompressible.

Table 5-2. Stirring Reynolds number, Re_M , for the investigated stirring speeds.

Stirring speed (min^{-1})	$Re_M (-)$
250	701.8
500	1403.6
1000	2807.1

The main difference between the standard $k-\epsilon$ and realisable $k-\epsilon$ models can be found in the calculations of eddy viscosity. In the standard $k-\epsilon$ model, the eddy viscosity is based on a constant dynamic viscosity coefficient (C_μ), while in the realisable $k-\epsilon$ model, a non-constant value for C_μ that allows for a more realistic representation of turbulence characteristics under varying flow conditions, is considered [442]. The reason why the realisable $k-\epsilon$ turbulence model was chosen instead of the standard $k-\epsilon$ model is its improved predictions for boundary layer characteristics in scenarios involving significant pressure gradients, separated flows, and recirculation [443].

$$\rho(\mathbf{u} \cdot \nabla)\mathbf{u} = \nabla \left(-P\mathbf{I} + (\mu + \mu_T) \nabla(\mathbf{u} + (\nabla\mathbf{u})^T) \right) + \mathbf{F} \quad (5-4)$$

$$\rho \nabla \cdot \mathbf{u} = 0 \quad (5-5)$$

The transport equation for k reads as

$$\rho \frac{\partial k}{\partial t} + \rho \mathbf{u} \cdot \nabla k = \nabla \left(\left(\mu + \frac{\rho C_\mu k^2}{\sigma_k \epsilon} \right) \nabla k \right) + \mu_T [\nabla \mathbf{u} : (\nabla \mathbf{u} + (\nabla \mathbf{u})^T)] - \rho \epsilon \quad (5-6)$$

The transport equation for ϵ is

$$\rho \frac{\partial \epsilon}{\partial t} + \rho \mathbf{u} \cdot \nabla \epsilon = \nabla \left(\left(\mu + \frac{\rho C_\mu k^2}{\sigma_\epsilon \epsilon} \right) \nabla \epsilon \right) + C_{1\epsilon} \rho s \epsilon - C_{2\epsilon} \rho \frac{\epsilon^2}{k + \sqrt{\nu \epsilon}} \quad (5-7)$$

Where, $\mathbf{u}$ the vector of the velocity, P is the pressure, $\mathbf{I}$ is the unit tensor, μ the fluid viscosity and $\mathbf{F}$ the external body forces that act on the fluid. The values of the turbulence parameters C_μ , σ_k , σ_ϵ , $C_{1\epsilon}$, $C_{2\epsilon}$, used were the ones reported by Shih et al. [444]. Due to the flow being isothermal and incompressible gravity was not included in the simulations (its effect was later tested and was found negligible), and since no other external forces were exerted on the fluid, $\mathbf{F}=0$. The flow was set as fully developed at the reactor inlets with a constant inlet flowrate and

the no-slip boundary conditions were applied at the reactor's walls and the external surface of the stirring bar.

The frozen rotor approach, also known as Multiple Reference Frame (MRF), is an approximate steady-state processing method and it is easily understandable if the whole mathematical approach is simplified into a rotating wall boundary condition [445]. In this case, the solid body is rotating around its axis of rotation, while the velocity, near the wall, has an $\omega \times r$ component, where ω is the angular velocity and r is the distance from the axis of rotation. Therefore, Equations 5-8 to 5-11 are solved in both the rotating and the stationary coordinate system, respectively. Subsequently, the frozen rotor approach requires two domains, one that is rotating (in this work, a cylindrical volume that engulfs the impeller as shown in Domain 1 of Figure 5-4) and one that is stationary (in this work, a cylindrical volume that occupies the remainder of the tank, including the two inlets and the outlet, denoted by Domain 2 in Figure 5-4). The data at the interface of the two domains are passed by interpolation, via imposing a boundary condition of fluid continuity [446]. The computation was considered as converged when the residuals that represent the difference between the computed estimates and the actual values, fell below the threshold of 10^{-4} . A transient sliding mesh study (where Domain 1 is rotating with time), was, also, conducted for one simulation to compare how well the MRF steady-state approximation captured the hydrodynamics. It was found that the MRF method was producing a very similar 3D velocity profile with the transient simulation, slightly overestimating the momentum diffusivity that resulted in expansion of the vortices formed at the wake of the stirring bar. However, the computational cost required to solve the transient model was significantly higher in comparison to the MRF steady-state approach (the transient simulation required > 48 hours for 4 impeller rotations; whilst using the same mesh, the MRF approach required 5 hours), and therefore the latter was applied. Further information on the transient study results can be found in Appendix C.

To guarantee the accuracy of the solution, while also minimising the computational time required for each simulation, a mesh independence study was performed. The number of grid nodes in the x, y and z directions in both the inner and outer mesh zones were systematically increased throughout the vessel such that three grids were generated – a medium, a refined medium (with enhanced boundary layers on the stirring arms and tank walls) and a very fine – comprising 2,906,804, 4,504,250 and 13,592,961 elements, respectively. The velocity magnitude along the tank radius at an arbitrary height of 9 mm from the tank bottom (and, respectively, 1 mm above the impeller) for the medium and the very fine mesh is presented in Figure 5-5. The difference in the velocity and turbulent energy dissipation rate between the investigated meshes can be found in Table 5-3. Based on the results of Figure 5-5 and the

reported values of Table 5-3, the medium mesh describes the velocity profile satisfactorily. However, to minimise the error in the minimum velocity and dissipation rate, a slightly refined version of it, consisting of 4,504,250 elements, was chosen for all simulations.

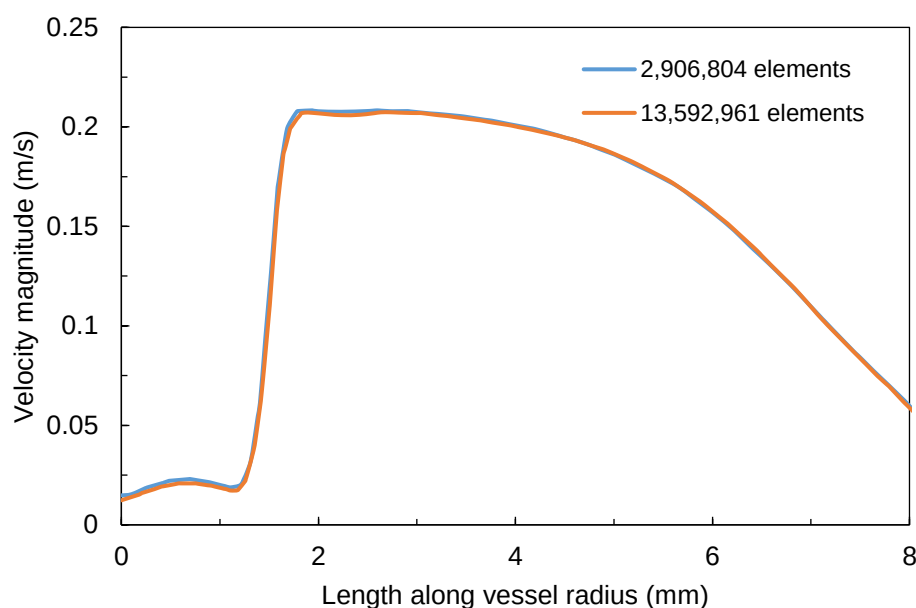


Figure 5-5. Velocity magnitude profile along the radius in the 2.35 mL stirred tank (9 mm distance from the tank bottom) for meshes of increasing number of elements at 500 rpm rotation frequency and 4 mL/min inlet flowrate.

Table 5-3. Average, maximum and minimum velocity magnitude in a line along the tank diameter, the volume average turbulent dissipation rate and their relative error, calculated by comparing the results obtained with the medium mesh to those obtained with a very fine mesh.

	Number of elements		Relative error
	2,906,804	13,592,961	
Maximum velocity (m/s)	0.2083	0.2082	0%
Minimum velocity (m/s)	0.0052	0.0046	13%
Average velocity (m/s)	0.1225	0.1284	5%
Volume average turbulent dissipation rate (m^2/s^3)	0.0389	0.0423	8%

5.2.3. Reaction kinetics acquisition

5.2.3.1. Reaction and experimental set-up

To demonstrate the ability of the miniaturised CSTR to precisely monitor reactions via coupling with Raman spectroscopy, a well-understood chemistry where the reagents and products were Raman active, with clear and separate peaks throughout the spectrum, was selected; the synthesis of *n*-benzylidenebenzylamine from benzaldehyde (ReagentPlus, 99%, Sigma-

Aldrich) and benzylamine (ReagentPlus, 99%, Sigma-Aldrich) in methanol (>99%, Fischer Scientific) [67, 68, 447, 448], as shown in Figure 5-6.

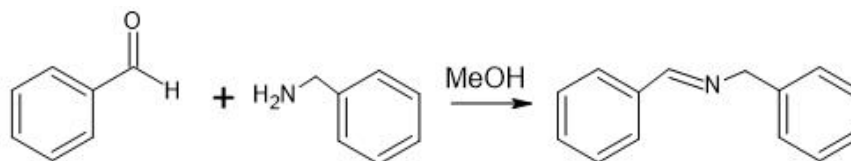


Figure 5-6. Imine synthesis employed as a test reaction for the m-CSTR coupled with Raman spectroscopy.

The synthesis of *n*-benzylidenebenzylamine followed a second order reaction rate, as shown in Equation 5-8.

$$-r_{BAI} = kC_{BAI}C_{BAm} \quad (5-8)$$

Where, k is the reaction rate constant ($\text{m}^3 \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$), C_{BAI} is the concentration of benzaldehyde (mol/m^3) and C_{BAm} is the concentration of benzylamine (mol/m^3).

Feeding the two reactants in a stoichiometric ratio of 1:1, allowed for the simplification of the reaction rate to Equation 5-9.

$$-r_{BAI} = kC_{BAI}^2 \quad (5-9)$$

Figure 5-7 shows a simplified schematic of the imine synthesis set-up. Two glass syringes (25 mL each, CETONI) were separately filled with a solution of benzaldehyde in methanol and benzylamine in methanol (2 M each 1:1 stoichiometric ratio). Another glass syringe (25 mL, CETONI) was filled with methanol and acted as the dilution stream for one of the reactants. All syringes were mounted on a Nemesys medium-pressure syringe pump (CETONI). The inlet concentrations of benzaldehyde and benzylamine entering the reactor were determined by the relative pump flow rates. Mixing in the reactor was achieved by adjusting the rotation frequency of the magnetic stirrer-hotplate (Stuart, Cole-Palmer LLC). To ensure isothermal operation, the feed was preheated using a digital magnetic stirrer-hotplate (IKA, RCT 5 digital), a cooling/heating circulator (Huber CC-K6) was connected to the reactor's jacket system ports and water was pumped continuously. A type K thermocouple (RS PRO) was inserted at the outlet of the reactor through a T-junction (IDEX) for continuous temperature monitoring of the reacting mixture by connecting it to an Arduino control box. An Adafruit thermocouple amplifier (Max31855) was soldered to a stripboard alongside an Arduino Nano and communication was established via SPI protocol. The Arduino outputted serial data including the internal temperature of the Adafruit and the temperature of the K-type thermocouple attached to the Adafruit. This serial data stream was then read in LabVIEW. The temperature of the water bath was adjusted accordingly by fine-tuning Huber's setpoint using a PID controller. Details

regarding the parameters of the PID controller and the integration of Huber in LabVIEW can be found in Appendix C. The reaction mixture was collected into a waste vessel (Festo).

To prevent evaporation of the solvent, the entire system was pressurised to 1 barg with nitrogen (BOC) using a mass flow controller (SLA mass flow controller, Brooks), a gas pressure sensor (Honeywell 40PC, 250 psig) and a back-pressure regulator (Swagelok K series, 250 psig), connected to the waste vessel. The back pressure regulator ensured that the pressure in the waste vessel was no lower than a certain value, while also working as pressure relief valve, expelling excess gas. One pressure relief valve (IDEX U-456, 100psi) was installed right after the reactor outlet to avoid overpressure above 7 bar, as the glass syringes used can withstand up to 10 bar.

The Raman probe (MarqMetrix) was mounted in a 3D-printed custom-made holder for reproducible sampling and placed on top of the reactor's window, which allowed for real-time inline monitoring of the reaction. The excitation wavelength for the Raman laser was 785 nm, the integration time was 500 ms and the laser power was set to 300 mW. After steady state was reached (3-5 reactor residence times), each experimental data point was determined by 5 consecutive Raman measurements, each consisting of an average of 10 scans.

The experimental process was automated using the Laboratory Virtual Instrument Engineering Workbench (LabVIEW) environment [276]. The LabVIEW code, developed in this work, allowed the user to run a set of experiments by setting the temperature, feed concentration and total flowrate at the user interface panel. For visualisation, the temperature and pressure trends of the system were also displayed in real time in graph charts, similar to the ones reported in Appendix B for the levulinic acid esterification experimental set-up (Chapter 4). The software featured an overheating and overpressurisation safety limit, which were set to 80 °C (to prevent water evaporation in the HUBER circulator) and 2 barg respectively and would automatically stop the experiment if these values were exceeded.

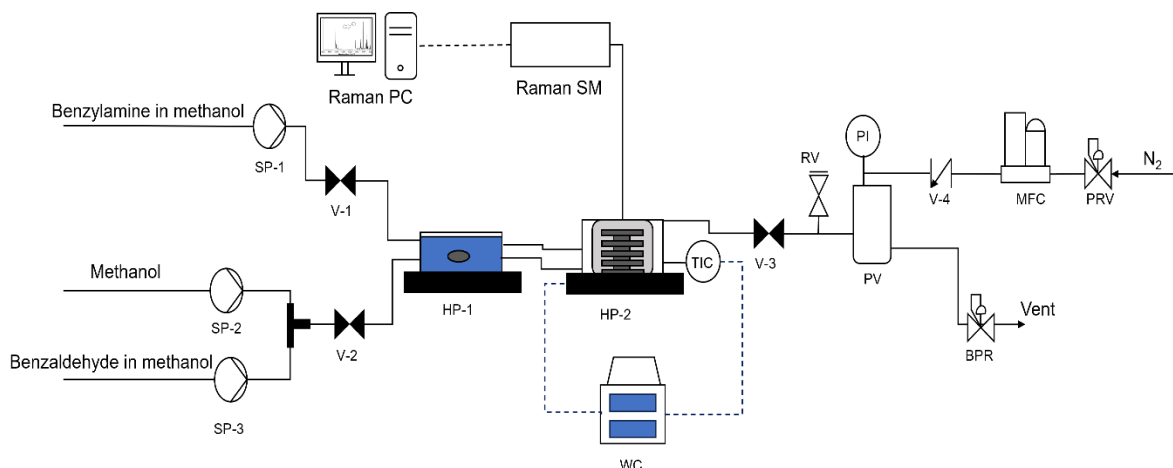


Figure 5-7. Experimental set-up for the kinetic data acquisition of the *n*-benzylidenebenzylamine synthesis. SP: syringe pump, SM: spectrometer, WC: water recirculator, HP: hotplate-stirrer, SP: syringe pump, PRV: pressure reducing valve, RV: pressure relief valve, MFC: mass flow controller, PV: pressure vessel, PI: pressure indicator, BPR: back pressure regulator, V: valve, TIC: temperature indicator-controller. All temperature, pressure and flow equipment were controlled by LabVIEW.

For the design of steady-state experiments, a Factorial Design (FD) using three factors (flowrate, temperature, and inlet concentration of benzaldehyde) with two levels per factor was employed, which resulted in 8 experimental conditions. Additionally, a mid-range temperature was investigated to confirm the validity of the model bringing the total number of experimental conditions to 12. The bounds of the design space were dictated by constraints in the experimental platform. Residence times were constrained by the accuracy range of the syringe pumps, which applied pressure on 25 mL glass syringes, dispensing through the system under 1 barg backpressure and by the rate of syringes emptying. It was experimentally shown that the 25 mL glass syringes could not pump accurately below 80 $\mu\text{L}/\text{min}$, therefore the lower inlet flowrate investigated was chosen equal to 0.5 mL/min. The higher flowrate for completion of the experiments within one experimental cycle without the need for a refill was set at 2 mL/min. The temperature range was determined based on the cooling/heating ability of the system, where water was used as the running medium and the solvent boiling point. The minimum and maximum temperatures were set at 15 $^{\circ}\text{C}$ and 45 $^{\circ}\text{C}$, respectively. The investigated design space is graphically presented in Figure 5-8 and the experimental conditions are also reported in Table 5-4. The campaign of experiments was conducted in three replicates, thus allowing to establish the robustness and reproducibility of the system.

Table 5-4. Experimental conditions investigated for the synthesis of *n*-benzylidenebenzylamine in methanol in steady-state experimentation.

Exp.	Flowrate (mL/min)	Temperature (°C)	Inlet concentration (M)
SS1	2	15	0.5
SS2	2	15	1
SS3	0.5	15	0.5
SS4	0.5	15	1
SS5	2	30	0.5
SS6	2	30	1
SS7	0.5	30	0.5
SS8	0.5	30	1
SS9	2	45	0.5
SS10	2	45	1
SS11	0.5	45	0.5
SS12	0.5	45	1

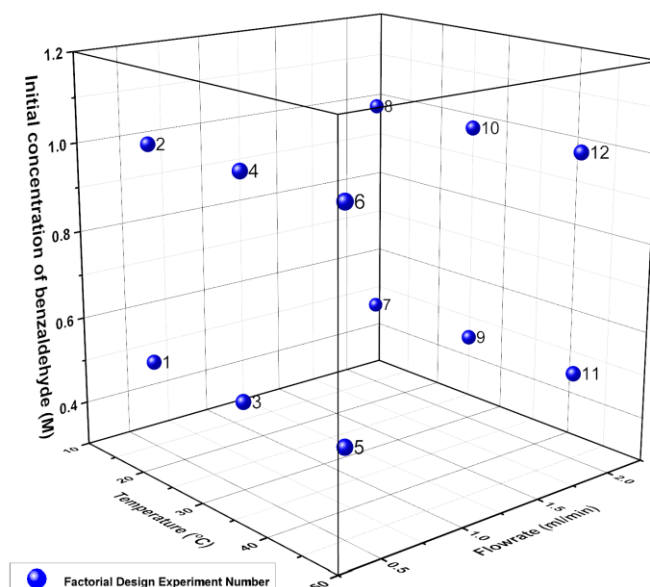


Figure 5-8. Experimental design space.

5.2.3.2. Post-processing of Raman spectra

The concentration of the reactants and products was calculated based on the area of the characteristic C=O stretching of the benzaldehyde at 1680–1730 cm^{-1} and C=N stretching of the *n*-benzylidenebenzylamine at 1630–1670 cm^{-1} (benzylamine does not display distinctive peaks), as shown in Figure 5-9. Prior to this, the calibration curves for the respective compounds were created. Since Raman spectra often contain both the desired signal as well as undesirable elements, such as baseline drift and random noise, baseline correction was an important step to extract the true Raman peak intensities for qualitative analysis. For this reason, a MATLAB script containing the airPLS algorithm [449] was employed that provided a simple and fast estimation of the baseline, requiring only the tuning of a single parameter to ensure baseline smoothness of all recorded spectra. Further details on the Raman spectra post-processing procedure, as well as the produced calibration curves, can be found in Appendix C, Section C4.

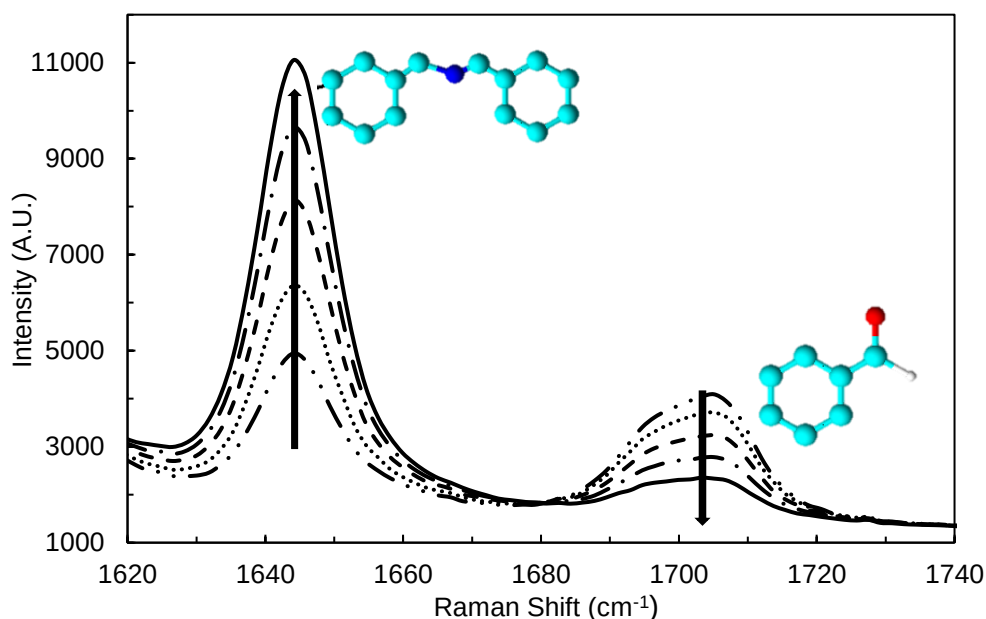


Figure 5-9. Recorded spectra of benzaldehyde (right peak) and *n*-benzylidenebenzylamine (left peak) monitored by inline Raman as the reaction progressed.

5.2.4. Modelling and parameter estimation of steady-state experiments

5.2.4.1. Design equations for a m-CSTR

A steady-state, isothermal CSTR of constant volume can be modelled using Equation 5-10.

$$Q \cdot (C_{BAI,0} - C_{BAI}) - kC_{BAI}^2 \cdot V_0 = 0 \quad (5-10)$$

where, $C_{BAI,0}$ is the concentration of benzaldehyde at the inlet (mol/m³).

5.2.4.2. Parameter estimation

As the m-CSTR was designed for rapid and reliable acquisition of reaction kinetics, the final goal of this Chapter was to accurately determine the reaction rate constant, k . To achieve this, k was expressed in the reparametrised Arrhenius form with two parameters KP_1 and KP_2 [260], as shown in Equations 5-11, 5-12 and 5-13, respectively.

$$k = Ae^{-\frac{E_\alpha}{RT}} \quad (5-11)$$

$$A = e^{-KP_1 + \frac{KP_2 \cdot b}{R \cdot T_M}} \quad (5-12)$$

$$E_\alpha = KP_2 \cdot b \quad (5-13)$$

Here, T is the reaction temperature (K). b is a scaling factor, and T_M is the reference temperature (K), calculated as the average value of the upper and lower temperature limits of the experimental conditions.

The results of the parameter estimation for KP_1 and KP_2 were analysed in terms of estimated values and statistics to quantify both the precision of the estimates and model's goodness of fit. Precision was assessed using Student's t -test statistics, the t -value at the 95% confidence level of each kinetic parameter should exceed the tabulated reference t -value given by a Student t -distribution [450]. Model fitting quality was evaluated using chi-square (χ^2) statistics, where the χ^2 value should be lower than the 95% reference value from statistical tables for the correct number of degrees of freedom [451]. For this reason, Equations 4-11 to 4-17 (used in Chapter 4 to describe the statistical models) were employed. The standard deviation of the measurement error for each response variable (concentration of benzaldehyde, C_{BAI} and concentration of n -benzylidenebenzylamine, C_{BIIm}), was calculated using the method of pooled standard deviation [452].

5.3. Results and discussion

5.3.1. RTD behaviour

To evaluate the deviation of the m-CSTR unit from perfectly mixed conditions, the RTD of the tracer in the m-CSTR was characterised at different stirring rotational speeds ($N = 250, 500$ and 1000 rpm) and inlet flowrates ($Q = 0.25, 1$ and 4 mL/min). Figure 5-10 shows the normalised RTDs, E_θ , where both inlets were used, for different flowrates and stirring speeds, plotted against the normalised residence time, θ , and compared to the ideal CSTR, the RTD of which is an exponential decay. As reports on the RTD of reactors with multiple inlets are scarce [96, 453-455], to test the assumption of ideal CSTR behaviour, in Figure 5-11a and Figure 5-11b, E_θ , for single inlet conditions, is also presented.

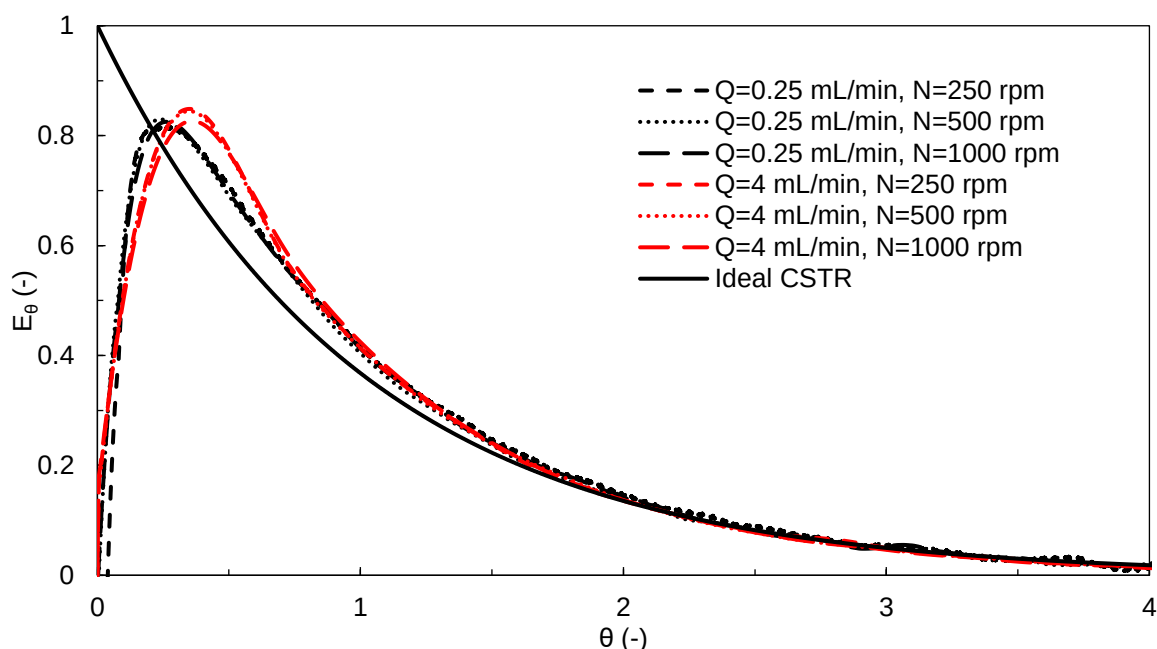


Figure 5-10. E_θ (reactor response) RTD curve of the 2.35 mL m-CSTR operating with two inlets for a total flowrate of $Q = 0.25$ mL/min and 4 mL/min at $N = 250, 500$ and 1000 rpm vs normalised residence time, θ , compared to the ideal CSTR model.

From Figure 5-10, it was observed that for both the lower (0.25 mL/min) and the higher (4 mL/min) total flowrate, the normalised RTDs follow near-ideal CSTR behaviour, with an average $RMSE_{RTD}$ of 8% (Equation 5-3), which is mostly visible in the part of the curve between $0 \leq \theta \leq 1.5$. The slight deviation of the two-inlet system was, also, reflected in the experimentally calculated residence times, which are presented in Table 5-5. The graphical representation of E_θ , when juxtaposed with the calculated residence times, highlighted an improvement in the macromixing quality with increasing stirring speed. The disparity between experimental and theoretical residence times for the two-inlet system could be attributed to two key factors. Firstly, there might exist a tiny mixing zone where the two inlet streams initially combine, creating a jetting stream, before fully incorporating into the reactor. Additionally, dispersion effects within the section extending from the injection point (located at the tip of the ferrule tightening the milli-fluidic tube through which the reagents flow, connecting the syringe pump with the reactor) and the reactor chamber could contribute to the discrepancy. It is also possible that a synergistic effect of both phenomena is influencing the observed residence times. Considering the E_θ for the single inlet system, depicted in Figure 5-11, the influence of the mixing zone diminished and dispersion in the channel between the injection point and the stirred region decreased with increasing flowrate. Consequently, the hydrodynamics of the m-CSTR tend towards ideal conditions and appear to be independent of the stirring speed for values exceeding 500 rpm.

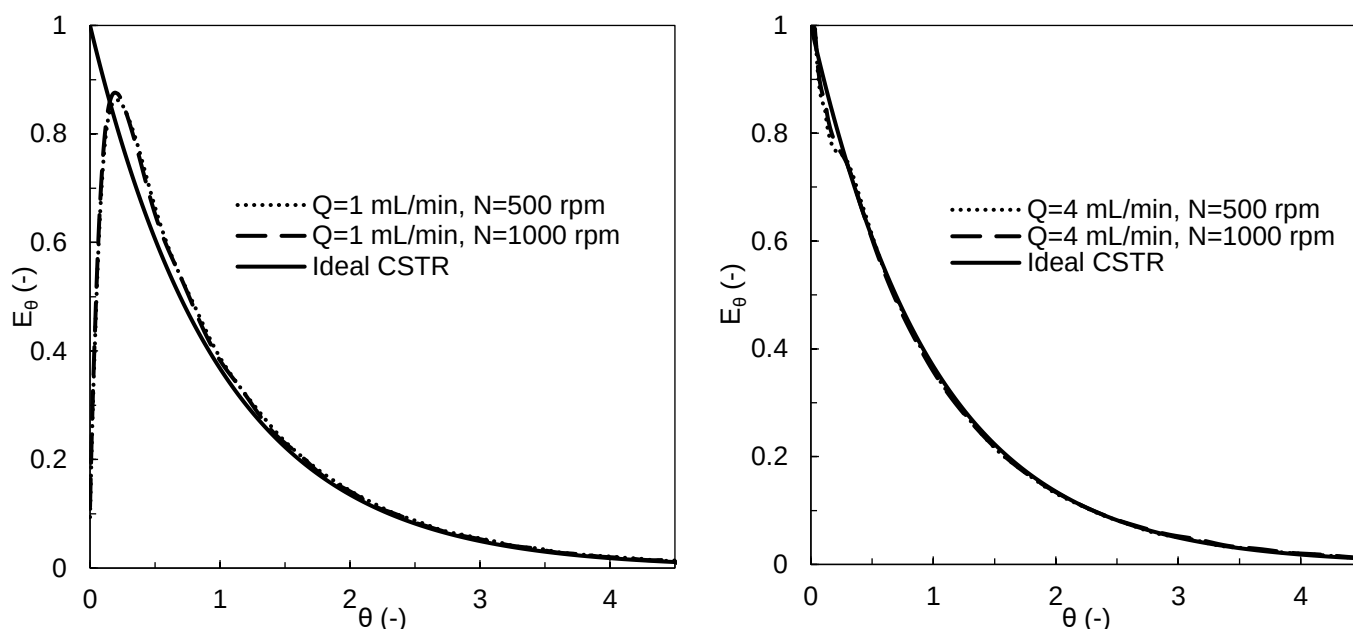


Figure 5-11. E_θ (reactor response) RTD curve of the 2.35 mL m-CSTR operating with a single inlet for a total flowrate of (a) 1 mL/min and (b) 4 mL/min at 500 and 1000 rpm compared to the ideal CSTR model.

Table 5-5. Theoretical mean residence time, τ , vs experimentally calculated mean residence time, $\bar{t}$, for different stirring speeds and percentage of recirculation, calculated based on Equation 5-12.

	Stirring speed (rpm)		
	250	500	1000
Theoretical mean residence time, τ (s)	Experimentally calculated mean residence time, $\bar{t}$ (s)		
579	634	629	625
145	160	160	157
36	41	39	38

Taking into consideration the complex hydrodynamics due to the confinement of the flow in the small tank, the assumption of nearly ideal CSTR behaviour is reasonable. The agitation provided by the custom-made magnetic impeller was sufficient to achieve rapid mixing and replicated the characteristics of a perfectly mixed tank, especially in the case of a single inlet. For optimal operation of m-CSTR with both inlets, operational guidelines have been delineated, stipulating a total inlet flowrate exceeding 0.25 mL/min and a stirring speed surpassing 500 rpm.

5.3.2. Microscale mixing in the reactor chamber

The stirring speed, denoted as N , varied between 250 and 1000 rpm and equal flowrates ranging from 0.25 mL/min to 2 mL/min (total flowrate Q of 0.5 mL/min and 4 mL/min) were investigated. The PTFE custom-made impeller and the cross-stirring bar were tested and operated for water solutions with normal flowrate ratio, R , of acid to buffer solution equal to 1. The flowrate ratio, R , of the two mixed streams is a parameter that can be further investigated depending on the intended use of the system but was considered out of scope for the current work. In Figure 5-12, the segregated index, X_s , for the different stirring configurations and the two extreme flowrates is plotted against the stirring speed. In Figure 5-13a and Figure 5-13b, the micromixing time, t_m , calculated by the IEM model [117, 122] (as described in Section 2.1.3.2), is plotted against the rotational stirring speed for each impeller individually.

As shown in Figure 5-12, the maximum segregation index, X_s , of both systems was equal to 0.040, a value small enough to consider almost complete back-mixing conditions. Moreover, better micro-mixing was achieved at higher flowrates, which was due to the larger colliding momentum in the reactor chamber and stronger chaotic advection. As the value of N increased, a consistent pattern emerged, where the segregation index tended to decrease. This can primarily be attributed to the greater energy input into the fluid and the increased velocity gradient and shearing force within the impeller unit. The decrease was sharper between 250 and 500 rpm and with a less steep gradient for $N > 500$ rpm for the Reynolds

number studied, showing less sensitivity to the flowrate at larger N , where the shearing stress of the fluid by the rotating impeller and the high turbulent kinetic energy dissipation dominated the micromixing process.

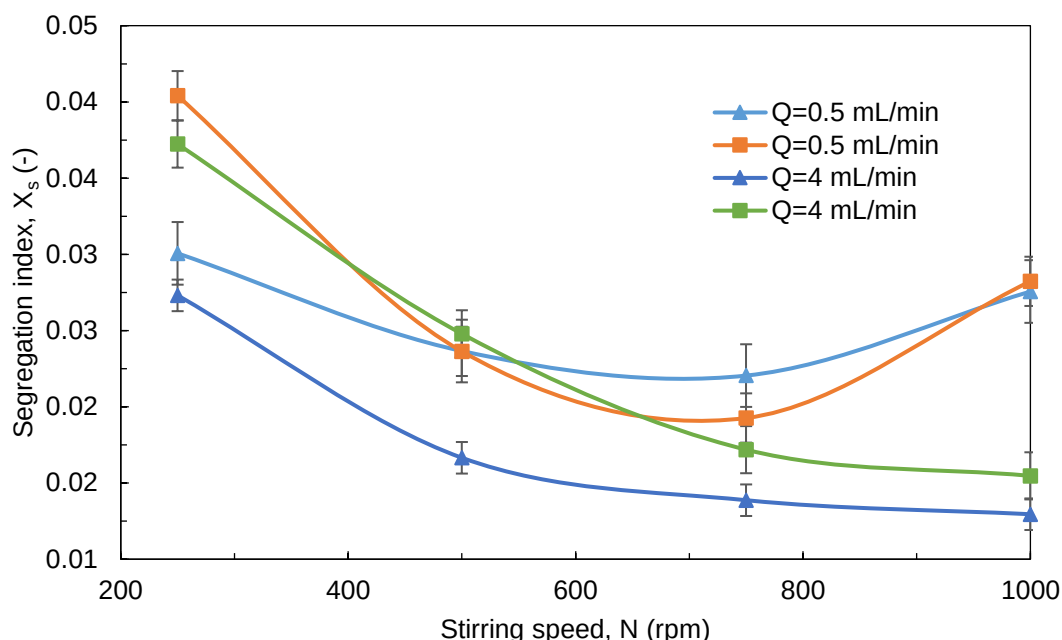


Figure 5-12. Segregation index, X_s , as a measure of the micromixing quality, vs the rotational stirring speed, N for flowrates of $Q=0.5$ and 4 mL/min for the two impeller configurations. The $\blacktriangle$ represent the custom-made impeller, and the $\blacksquare$ represent the cross-shaped stirring bar. Error bars are calculated based on the standard deviation of repeated measurements.

When comparing the two stirring configurations, the custom-made impeller outperforms the cross-shaped stirring bar in terms of segregation index, X_s , for almost all conditions studied. For the in-house fabricated impeller, for flowrate equal to 0.5 mL/min, the segregation index dropped by 21% between 250 and 500 rpm and demonstrated minimal sensitivity to variations in stirring speed between 500 and 750 rpm. For the cross-shaped stirring bar, the segregation index decreased by 41% (two-fold decrease in comparison to the slotted impeller) between 250 and 500 rpm and dropped further at 750 rpm. For both impellers at $N=1000$ rpm, an increase of the segregation index was observed. This increase may be attributed to an antagonistic effect of the inlet flow and the increased stirring rates. To offer further insight, in the case of $N=1000$ rpm, the impellers completed 16.67 rotations per second, which translated into 1 rotation per 6 milliseconds, a length of time similar to the micro-mixing time measured, as shown in Figure 5-12a and Figure 5-12b. Because of the reduced inlet energy of the fluid in lower flowrates, the molecules of the reactants did not have enough time to diffuse and react before they were removed from the reaction zone by the rapid stirring, a phenomenon responsible for the deterioration of the micromixing. This trend was less significant in the case of higher inlet velocities, based on the segregation index values for

flowrates equal to 4 mL/min, where X_s decreased up to 750 rpm and then remained independent of the stirring speed.

In examining Figure 5-13a and Figure 5-13b, it becomes apparent that for both stirring configurations, the effect of inlet flowrate on higher stirring speeds became progressively negligible. Moreover, the mixing time trends were less consistent in the case of the cross-shaped stirring bar (Figure 5-13b) in comparison to the slotted impeller (Figure 5-13a). This can be attributed to the geometrical characteristics of the cross-shaped impeller, the diameter, and the height of which were smaller than that of the reaction chamber. The difference in the dimensions may occasionally lead to displacement from the centre of the tank and more chaotic movement inside the vessel (i.e. interaction with the walls), especially when higher stirring speeds are used. Overall, as inferred from the preceding observations, the m-CSTR unit employing the slotted impeller achieved satisfactory micromixing conditions and displayed superior performance across the tested parameter ranges compared to the conventional cross-stirring bar. The value of t_m for the slotted impeller of the m-CSTR was in the same magnitude order with passive [112], gas-induced [456] and active mixers [96, 457, 458] where the Villermux-Dushman reaction framework was applied.

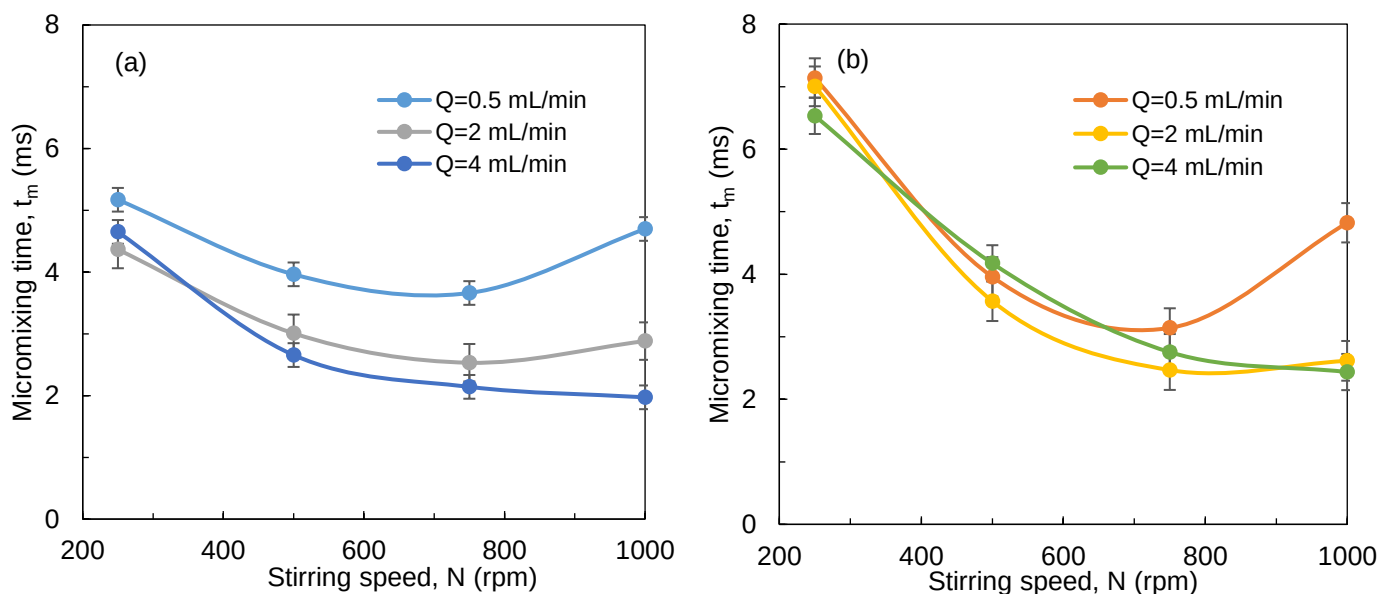


Figure 5-13. Micromixing time, t_m , vs the rotational stirring speed, N , for flowrates of $Q = 0.5, 2$ and 4 mL/min for (a) the in-house slotted impeller and (b) the cross-stirring bar. Error bars are calculated based on the standard deviation of repeated measurements.

5.3.3. m-CSTR hydrodynamics

5.3.3.1. Flow patterns in the reactor chamber

Due to the asymmetrical position of the reactor's inlets in relation to the impeller's rotation, upon entering the mixed tank, the inlet flow streams can either impinge on the tips of the stirring bar arms or flow into the curved space formed between two consecutive blades. Given the relatively low flowrates employed in this study, this entrance effect was expected to have minimal impact. To investigate the discrepancies in the development of the instantaneous velocity distribution with regards to the relative position of the impeller to the inlet, as the frozen rotor approximation captures only a moment of the impeller's rotation, the model was solved at two different rotation angles; one where the impeller was aligned with both inlets and the incoming fluid was met by the tips of the slotted stirring blades and one where the impeller was shifted at a 45° angle, allowing the fluid entering to interact with open space. Figure 5-14 presents the two steady-state impeller configurations.

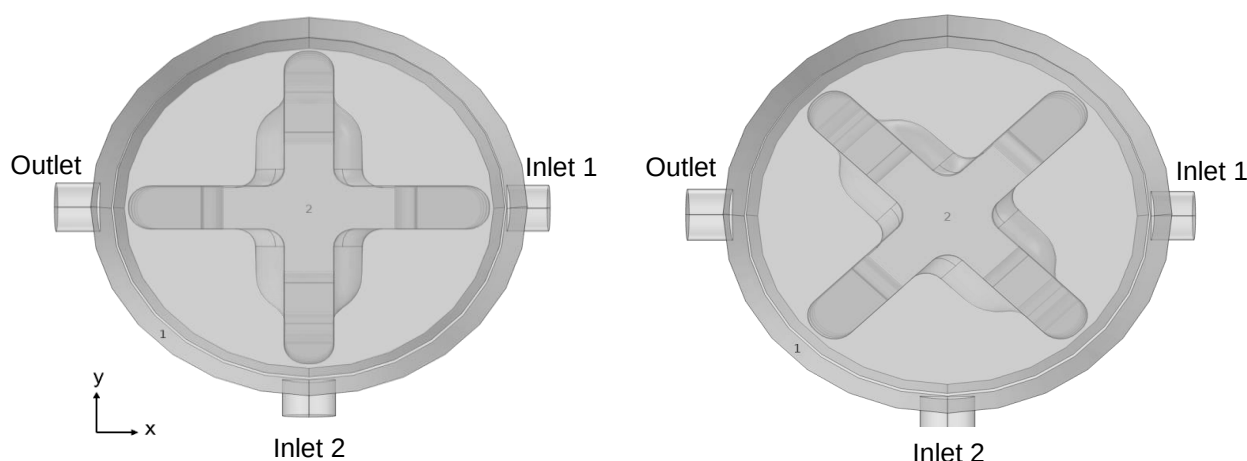


Figure 5-14. Position of the stirrer in MRF simulations with respect to the inlets: at 0° angle (left) and 45° angle (right).

The reported velocities for the 3-D geometry relative to the rotation axis are denoted as 'axial' (orange arrow), 'radial' (green arrow) and 'tangential' (blue arrow), as presented in Figure 5-15a. Figure 5-15b and Figure 5-15c illustrate a typical flow pattern on a xy-plane (plane parallel to the outlet) inside the 2.35 mL tank, when operating at 250 rpm with an inlet flowrate of 4 mL/min at a 0° and at a 45° angle, respectively. In all cases, when stirring was applied, the flow field was dominated by the tangential velocity component, which is associated with the rotational motion of the impeller. The maximum average fluid velocity was detected in the fluid directly in contact with the tips of the impeller, where the shear rate is the highest, as shown in Figure 5-15b and Figure 5-15c. Conversely, the minimum velocity was identified at the centre of the tank, directly above impeller and extending to the vessel's top. This trend suggested the possible formation of a vortex, akin to what is observed in open vessels [459].

The radial and axial velocity components were equally important for the mixing investigation, as they can map the presence of recirculation zones. Figure 5-16 shows the axial and radial velocity components, at planes perpendicular to the impeller at 250 rpm and flowrate of 4 mL/min for the case of 0° impeller rotation angle (Figure 5-16a and Figure 5-16b) and for the case of 45° impeller rotation angle (Figure 5-16c and Figure 5-16d). All vectors are normalised and colour-coded according to the magnitude of their average velocity vector tangential on each plane. As depicted in Figure 5-15, the magnitude of the radial and axial velocities was comparable to the scale of the strong swirling tangential velocity (Figure 5-15a and Figure 5-15b), almost half its value. This pattern was suggestive of effective mixing performance throughout both the vertical and horizontal dimensions of the vessel. Furthermore, the vector profiles in Figure 5-16 facilitate a direct comparative assessment of the impact of different impeller angles relative to inlet location. As anticipated, some variance was noted in the magnitude of the velocity vectors between the two cases. At 0° impeller angle, the inlet flow impacted the stirring bar arms, resulting in higher velocities near the tank walls compared to the slots forming between the wings of the impeller. At a 45° impeller angle, a more uniform velocity profile was observed with relatively high velocities along the depth of the reactor. Notably, in both instances, the prevailing flow pattern exhibited the formation of dual vortices above the impeller, one on each side. For simplification, the subsequent analysis and discussion will be grounded in the insights garnered from the 45° impeller angle configuration.

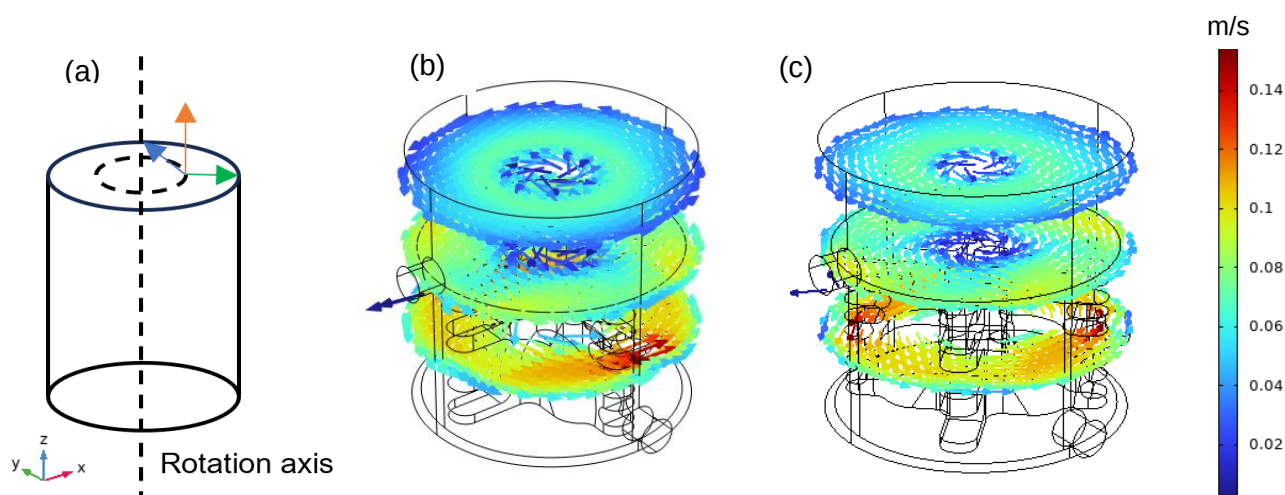


Figure 5-15. (a) Schematic view of the cylindrical geometry and the axis of rotation, with x, y, and z axes shown for spatial reference. Tangential velocity component ($Q = 4$ mL/min, $N = 250$ rpm) at (b) 0° impeller rotation angle (c) 45° impeller rotation angle. The colour-bars represent the xy velocity vector magnitude in m/s.

In Figure 5-17, the velocity vectors for the case of total flowrate of 4 mL/min and stirring speed of 250 rpm are displayed on two planes; a yz plane, which is perpendicular to the second inlet tank (Figure 5-17a) and a xz plane that is perpendicular to one of the inlets and the outlet of the tank (Figure 5-17b). An initial observation, based on Figure 5-17, was that the 2-D pattern flow resembled that produced by an axial-flow impeller in an open baffled tank [460].

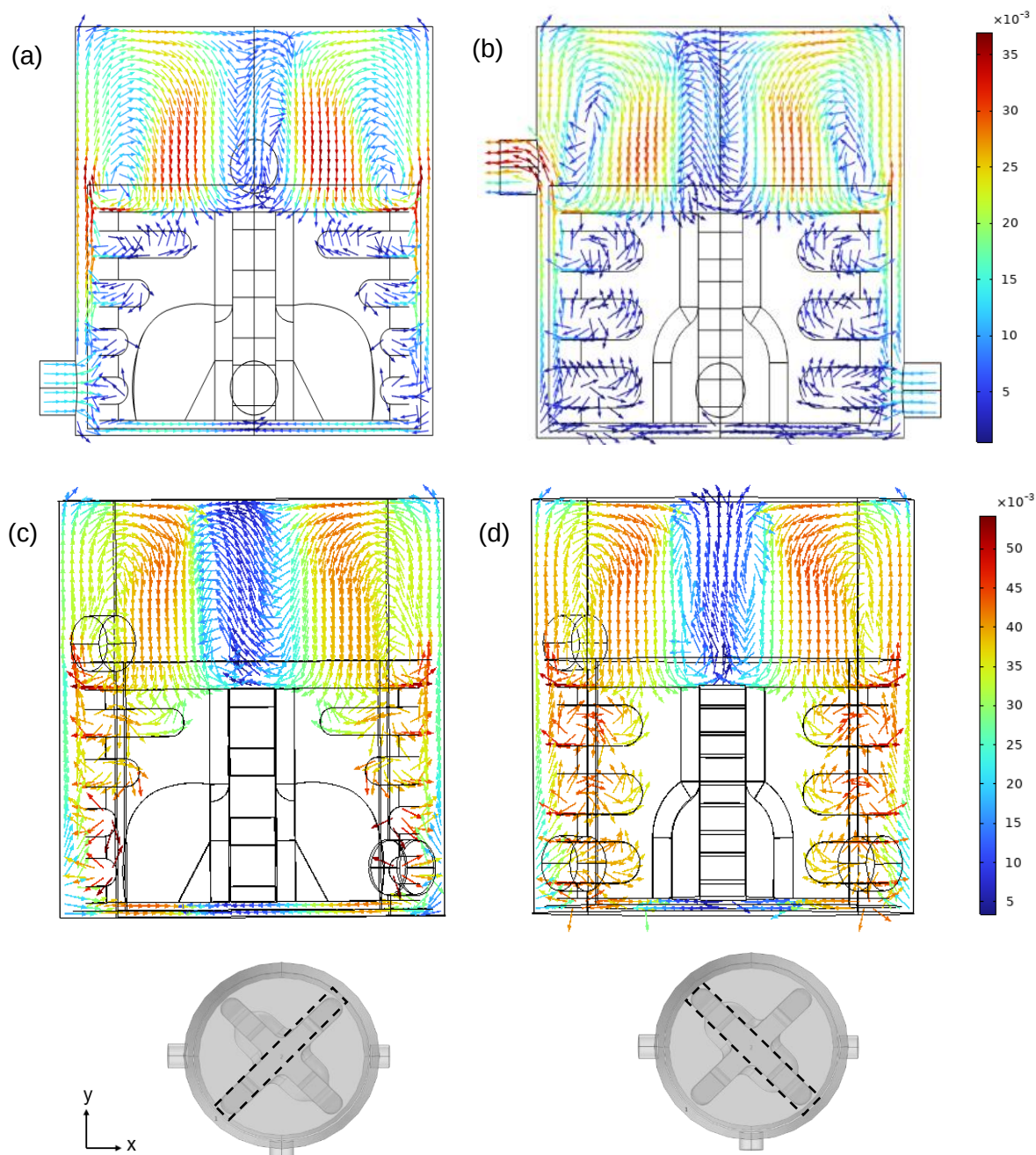


Figure 5-16. Flow pattern inside the 2.35 mL CSTR tank on planes tangential to the impeller for different stirring angles ($Q = 4$ mL/min, $N = 250$ rpm). (a,b) 0° angle and (c,d) 45° angle. The colour-bars represent the velocity vector magnitude in m/s. The dashed lines in the schematics of the impeller position represent the planes perpendicular to the impeller for visualisation purposes.

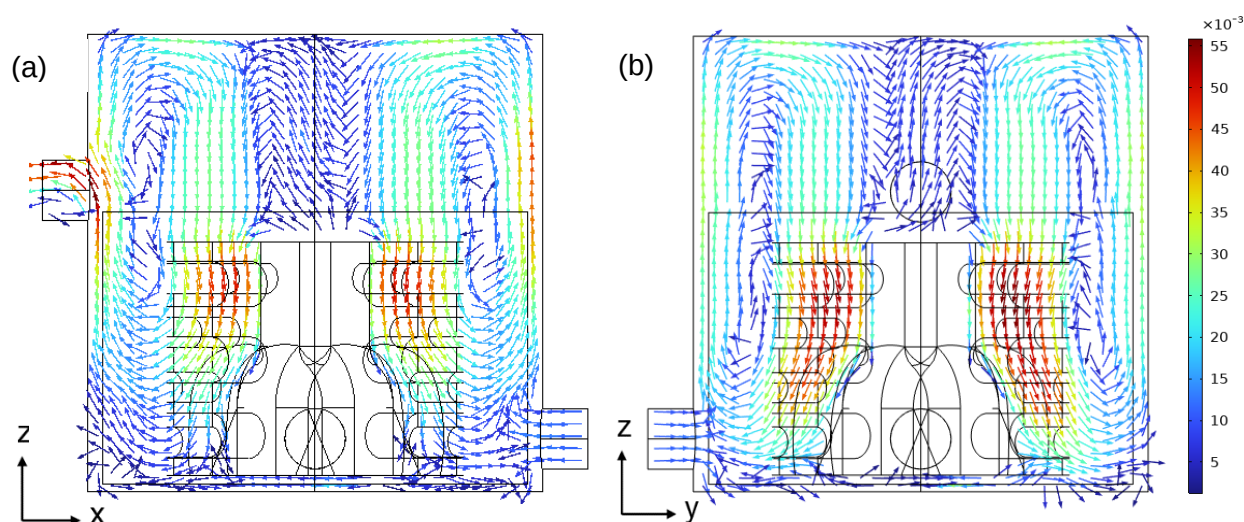


Figure 5-17. Flow pattern inside the 2.35 mL CSTR tank ($Q = 4$ mL/min and $N = 250$ rpm) (a) on the xz plane and (b) on the yz plane. The colour-bars represent the velocity vector magnitude on each plane in m/s.

The fluid was discharged from the impeller tips at its highest velocity and ascended in parallel with the walls until reaching the top, at which point it is redirected towards the vessel's centre, before recirculating back in the direction of the impeller. This flow pattern resulted in the formation of two regions of toroidal recirculation on both sides of the top part of the custom-made stirring bar. As part of the comparative analysis, flow patterns under various stirring conditions and flowrates were examined. In Figure 5-18, the radial and axial velocities were illustrated on the xz plane (plane parallel to both the inlet and the outlet). These profiles were captured at a constant stirring speed (Figure 5-18a & Figure 5-18b, Figure 5-18c & Figure 5-18d, Figure 5-18e & Figure 5-18f) at the two extremes of the inlet flowrate (0.25 mL/min and 4 mL/min). Based on the magnitude of the velocity profiles of Figure 5-18, it was observed that the most important parameter that dictated the flow pattern was the active stirring, with higher average velocities as the number of rpm increased, independent of the inlet flowrate. The fluid entering the tank was directly dispersed towards the edges of the tank, as previously described, following a similar flow pattern. However, in the area above the impeller, the flow exhibited a stronger tendency to move in chaotic order towards the centre of the tank as the stirring speed increased (based on the orientation of the velocity vectors). Although the condition of minimal backflow is imposed as a constraint at the outlet of the system, especially in the cases of lower flowrates, an extent of backflow was observed. This phenomenon can be computationally eliminated if the outlet length is extended, or by reorienting the outlet channel so it aligns better with the overall flow direction in this region. However, since the study was focused on the qualitative feature of the velocity field, the outlet feature was ignored.

Due to the unique geometry of the impeller that is composed of four stirring blades on one plane and five stirring blades on the other, it was also of interest to investigate the flow between the protruding fins. Since the flow depended strongly on the stirring speed, Figure 5-19 presents the flow profile on planes perpendicular to the cross-sections of the impeller, capturing the geometrical features of the stirring blades, for total flowrate of 4 mL/min and stirrings speeds of 250 and 1000 rpm. A close look at the velocity vectors in the gaps shows that the increased shear forces in the vicinity of the stirring blades (Figure 5-19c and Figure 5-19d), as a result of higher stirring speeds, tended to promote a more unidirectional flow pattern in comparison to lower stirring speeds (Figure 5-19a and Figure 5-19b). This effect was more obvious on the plane with four stirring blades (Figure 5-19d), in the first and second gap (counting from the bottom). These patterns were less pronounced in the case of smaller gaps (five stirring blades), where fluid tended to bounce back into the main flow (Figure 5-19c).

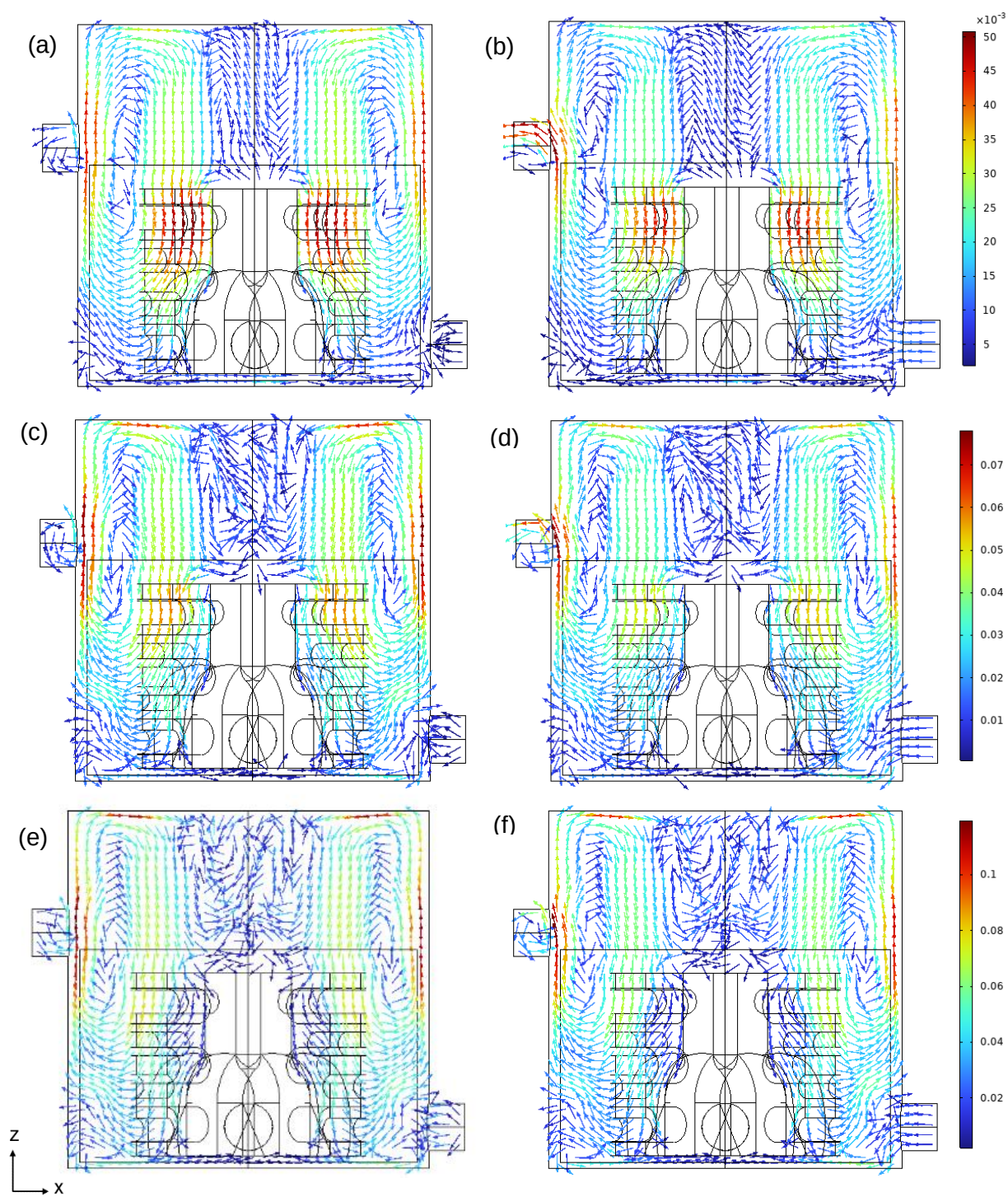


Figure 5-18. Flow profile inside the 2.35 mL CSTR tank on the xz plane for (a) $Q = 0.25$ mL/min, $N = 250$ rpm, (b) $Q = 4$ mL/min, $N = 250$ rpm, (c) $Q = 0.25$ mL/min, $N = 500$ rpm, (d) $Q = 4$ mL/min, $N = 500$ rpm, (e) $Q = 0.25$ mL/min, $N = 1000$ rpm and (f) $Q = 4$ mL/min, $N = 1000$ rpm. The colour-bars represent the xz velocity vector magnitude in m/s.

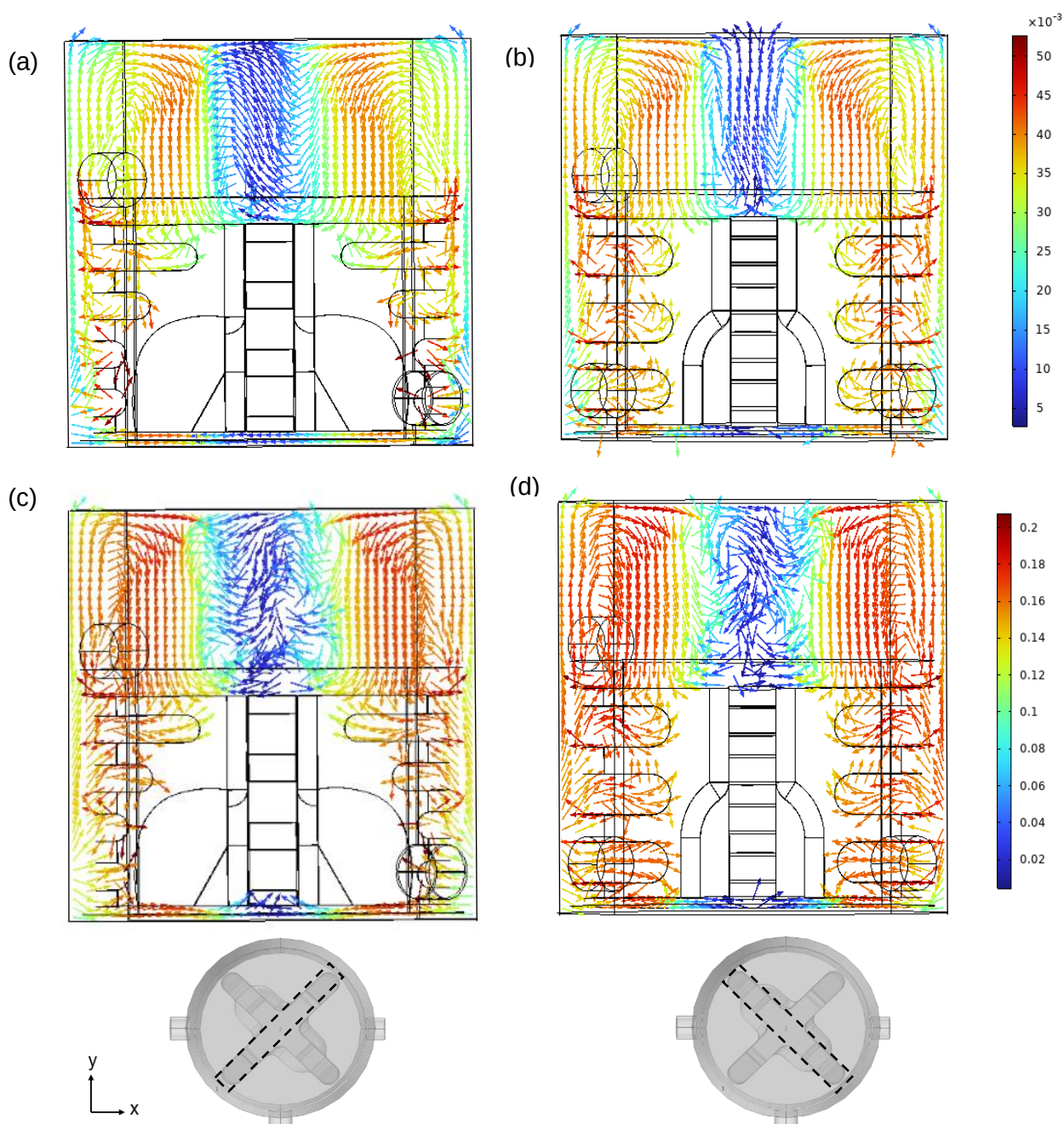


Figure 5-19. Flow pattern inside the 2.35 mL CSTR tank on planes perpendicular to the impeller's cross-sections (planes denoted by dashed lines in the schematics for $Q=4$ mL/min and (a,b) 250 rpm, (c,d) 1000 rpm. The colour-bars represent the velocity vector magnitude in m/s. The dashed lines in the schematics of the impeller position represent the planes perpendicular to the impeller for visualisation purposes.

5.3.3.2. Comparison of custom-made impeller to cross-shaped stirring bar

Lastly, a comparison of the hydrodynamics inside the tank between the cross-stirring bar and the slotted impeller was attempted. In Figure 5-20, the velocity contours at the wake of the two different impellers are presented for the low (Figure 5-20a and Figure 5-20c) and high values (Figure 5-20b and Figure 5-20d) of stirring speeds and flowrate of 4 mL/min. Based on Figure

5-20, it can be observed that the turbulence dissipation caused by the slotted impeller, which resulted in high fluid velocities far away from the stirring arms, was superior to this of the cross-stirring bar for the stirring speeds studied. The analysis of the flow patterns inside the m-CSTR provided valuable insight for the identification of potential dead zones and by-passing, and proved that the reactor configuration system allowed for vortices' formation that expanded along the height of the reactor chamber, a mechanism that further supports the experimentally proven mixing efficiency. The introduction of baffles could further increase the velocity in the radial and axial direction, with the risk of obstructing the free movement of the impeller. To establish the superiority of the custom-made impeller when it comes to macromixing, further RTD experiments of the vessel with the cross-stirring bar need to be pursued.

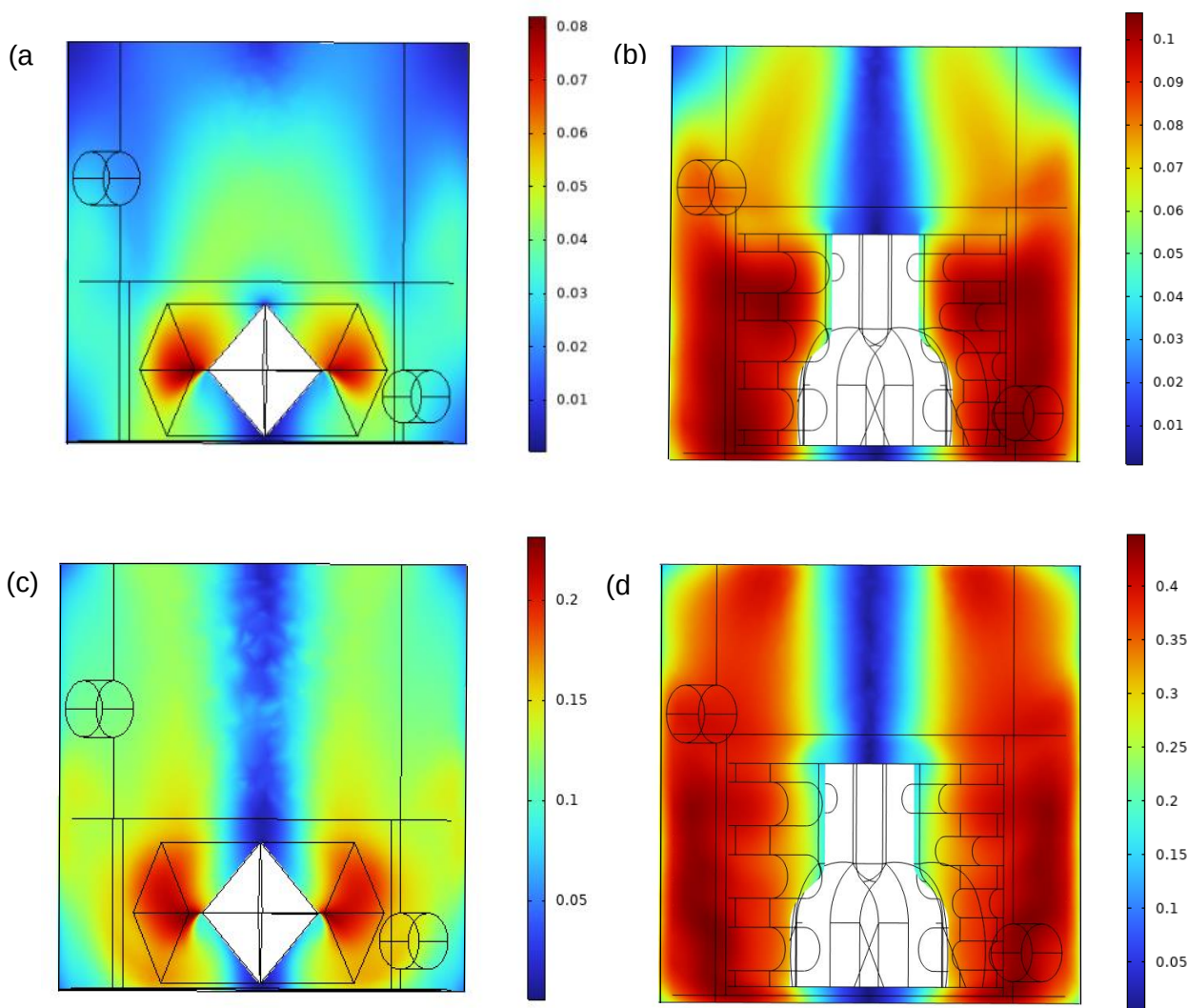


Figure 5-20. Velocity contour at the wake of (a) the cross-stirring bar at $N=250$ rpm, (b) the slotted impeller at $N=250$ rpm, (c) the cross-stirring bar at $N=1000$ rpm, (d) the slotted impeller at $N=1000$ rpm for $Q=4$ mL/min. The colour-bars represent the average velocity vector magnitude (taking into consideration all velocity components) in m/s.

5.3.4. Acquisition of reaction kinetics in flow using Raman spectroscopy

Parameter estimation results are presented in Table 5-6. Parameters KP_1 and KP_2 were estimated with good accuracy, based on their t-values and a good fitting of the experimental data to the model was granted, as the χ^2 -test was amply satisfied (i.e. $\chi^2 = 41.21 < 48.50$). The standard deviation of the measurement error was calculated from repeated identical experiments to be 0.017 M for benzaldehyde and 0.014 M for *n*-benzylidenebenzylamine, respectively. These standard deviations were used in the constant variance model for parameter estimation and can be attributed to the measurement system, as quantitative analysis using Raman spectroscopy with an open beam can be considered more sensitive to variations in the surrounding environment than a flow cell.

Table 5-6. Parameter estimation results for the reparameterised model including estimated value, standard deviation and 95% t-value.

Parameter	Value	Standard deviation	95% t-value
KP_1	3.47	0.05	76.63
KP_2	2.75	0.28	9.81
Reference t-value (95%)	1.69		
χ^2 ($\chi^2_{ref}=48.50$)	41.21		

From the results of Table 5-6, given the reparameterisation carried out in the original model through Equations 5-11 to 5-13, it was possible to calculate the kinetic parameters A and E_α of the original model, as detailed in Table 5-7.

Table 5-7. Estimated values of the parameters in the original kinetic model.

Parameter	Value
A ($L\ mol^{-1}\ s^{-1}$)	1652.67
E_α (kJ/mol)	27.43
k (at 25°C) ($L\ mol^{-1}\ s^{-1}$)	0.026

The adequacy of the 2nd order kinetic model is shown graphically in the parity plot of Figure 5-21, where the model predictions for the concentration of benzaldehyde fell around the interval of the maximum error, calculated as 2 times the experimental standard deviation.

Monitoring the progress of the formation of an imine, namely *N*-(1-phenylethylidene)-aniline, using offline Raman spectroscopy, was first reported by Lee et al. [461] who studied the reaction of aniline and acetophenone in chloroform. The reaction was studied over the course of 8 hours in a 200 mL volumetric flask for an initial concentration of 0.72 M for each reactant and temperatures between 25 and 45°C. The reaction was found to follow first order kinetics with respect to acetophenone and aniline and the reaction rate constant was equal to 0.00018

$\text{L mol}^{-1} \text{s}^{-1}$ at 25°C , which is, approximately, two orders of magnitude lower than the reaction rate constant of the synthesis of *n*-benzylidenebenzylamine, reported in this work.

The estimated kinetic data of the imine synthesis after performing steady state experiments were compared with reported values that can be found in Table 5-8. Fath et al. [67] investigated the reaction kinetics of the same reaction system in a coiled stainless steel microreactor of total inner volume of 1.87 mL, using an inline FTIR spectrometer at the end of the reactor. The kinetic data were estimated using two different approaches: previously determined calibration curves and chemometrics. Based on calibration, a reaction constant of $0.025 \text{ L mol}^{-1} \text{s}^{-1}$ was reported at 25°C , accompanied by an activation energy of 39.2 kJ/mol under steady-state conditions.

Schulz et al. [68], also investigated the synthesis of *n*-benzylidenebenzylamine in a nearly isothermal oscillating segmented flow reactor (where each 7 μL droplet behaved practically as a batch reactor), using Raman spectroscopy. Similarly to Fath et al. [67], chemometrics were employed to obtain calibration-free kinetic parameters. The reaction rate coefficient at 25°C was calculated equal to $0.036 \text{ L mol}^{-1} \text{s}^{-1}$ and the activation energy was 29.3 kJ/mol. The kinetic rate constant and activation energy in this work are of similar range to the ones reported by Fath et al. [67] and Schulz et al. [68]. The discrepancies between this work and the work of Fath et al. [67] can be attributed to the different reactor set-ups used and the explored design space, as the design space reported here was further expanded to include higher temperatures, different inlet concentrations of benzaldehyde were tested and the residence times were constrained between 1.2 and 4.6 minutes. Regarding the results of Schulz et al. [68], it was unclear if the volume of the pre-mixer and the time before reaching the temperature-controlled reactor was accounted for in the investigation of reaction kinetics.

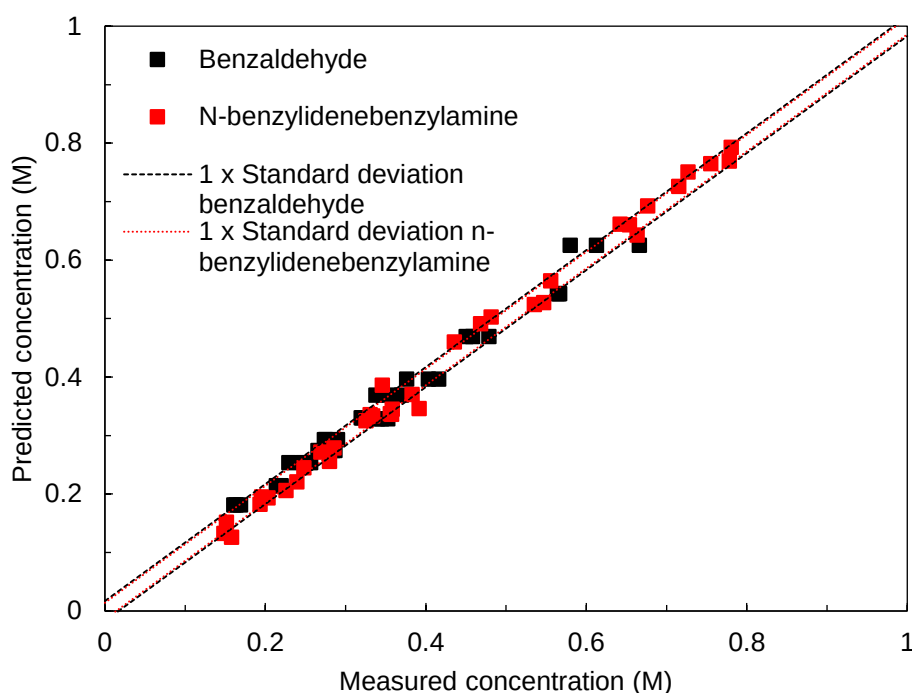


Figure 5-21. Parity plot for model-predicted and experimentally measured concentration of benzaldehyde and *n*-benzylidenebenzylamine. The dashed lines represent the one-standard deviation limits.

Table 5-8. Comparison of reported kinetic parameters for the synthesis of *n*-benzylidenebenzylamine.

Reactor setup	Temperature (°C)	Residence time (min)	$C_{\text{BAL},0}$ (M)	k at 25°C (L mol ⁻¹ s ⁻¹)	E_a (kJ/mol)
Coiled stainless steel microreactor (Fath et al. [67])	15-35	0.2 - 6	2	0.025	39.2
Oscillating segmented flow reactor (Schulz et al. [68])	15-45	/	1	0.036	29.3
m-CSTR (This work)	15-45	1.2-4.6	1	0.026	27.5

5.4. Conclusions

A miniaturised CSTR was fabricated and integrated into an automated LabVIEW-controlled platform, for determining reaction kinetics of an imine synthesis in a continuous flow system, employing inline Raman spectroscopy for real-time monitoring. The reactor assembly comprised a stainless-steel reactor chamber with a quartz glass window and an integrated heating jacket, enabling reaction control below room temperature. The design's flexibility in window selection and easy replacement rendered the reactor suitable not only for Raman spectroscopy but also for other spectroscopic techniques. The CSTR unit, designed for plug-and-play functionality, offers the versatility to acquire kinetics data within various configurations, including CSTR cascades or combinations of PFR and CSTR cascades. The custom-designed PTFE impeller ensured ideal CSTR behaviour when one and both inlets of the reactor were used, efficient micromixing performance and performed better when

compared to a conventional cross-shaped stirring bar of similar dimensions. The hydrodynamics of the reactor, specifically the velocity profile, were investigated using CFD. The study revealed that the custom-made impeller functioned as an axial impeller, generating swirling flow patterns that dominated the flow field across a wide range of inlet flow rates, with vortices extending throughout the reactor depth. The kinetic parameters of the second order *n*-benzylidenebenzylamine synthesis from benzaldehyde and benzylamine in methanol were determined, using Raman spectral data obtained directly from the inside of the m-CSTR, after being processed with a simple but efficient baseline correction methodology. The capability of the reactor to simultaneously operate as a stirred flowcell further expands its applicability for monitoring reactions involving solid formation/suspension, such as crystallisation reactions.

Chapter 6. Rapid kinetic parameter estimation via transient experiments in a miniaturised CSTR

6.1. Introduction

The integration of a m-CSTR with operando, non-invasive Raman spectroscopy was proven successful for model identification and accurate parameter estimation in the synthesis of *n*-benzylidene-benzylamine, as presented in Chapter 5. However, the experimental steady-state campaign was time-consuming requiring approximately 4-6 hours, due to the necessity of achieving steady-state conditions, before each measurement for every experimental condition investigated. Therefore, the aim of this chapter is to merge the speed of transient experiments with the rapid detection and quantification offered by spectroscopy to achieve precise parameter estimates in a significantly reduced timeframe.

A prevalent approach in transient kinetic studies involves manipulating flow conditions at selected temperatures. Mozharov et al. [9] employed a step change in flowrate to investigate a Knoevenagel condensation reaction using inline non-invasive Raman spectroscopy. However, limitations arose as the kinetics extraction relied on estimating the onset and conclusion of transient flow. The same test reaction was employed by Wyvratt et al. [462], where a non-linear sinusoidal dynamic ramp was imposed, but the approach presented experimental challenges and did not demonstrate notable advantages when compared to linear ramps. Moore and Jensen [361] enhanced the step-change method by incorporating an exponential flowrate ramp in the study of a Paal-Knorr pyrrole synthesis, enabling more precise tracking of reaction times through the use of infrared spectroscopy. Schwolow et al. [176] adopted a similar gradual flowrate change in their in-situ Raman-equipped microreactor setup to rapidly gather kinetics data for a Michael addition reaction. Building on this, Hone et al. [350] applied the methodology to a multistep SNAr reaction, demonstrating its robustness for complex mechanisms and assessing the impact of dispersion in these systems. Drawing inspiration from Moore and Jensen's [361] methodology, Fath et al. [67] conducted comparative parameter estimations for the synthesis of *n*-benzylidene-benzylamine through steady-state and nonsteady-state ramp experiments, with continuous monitoring of IR spectra. Herck and Junkers [463] adopted the timesweep approach leveraging the period immediately following a sudden change in flowrate for the screening of the RAFT polymerisation by using a benchtop NMR. An automated flow reactor platform with a machine learning technique for model discrimination and identification of the correct kinetic parameters based on experimental data generated by flowrate ramps coupled with online HPLC analysis was proposed by Taylor et al. [353]. Their study focused on the reaction of phenol with acetyl chloride, as well as the sequential reactions of 4-aminophenol with acetic anhydride, forming paracetamol, followed by consecutive reactions leading to diacetamate and the synthesis of metoprolol.

Temperature serves as another manipulated variable in transient experiments, with Wojciechowski [464] introducing the concept of temperature scanning plug flow reactors (TSPFR) for swift kinetic investigations across a broad temperature range. Kolkowski et al. [465] used the same reactor for parameter estimation in various reactions, including the oxidation of carbon monoxide, steam reforming of methanol, and oxidative dehydrogenation of propane.

Although a richer mapping of the design space could be achieved by applying both temperature and residence time changes simultaneously, little work has been published due to the complexity arising from the choice of experimental setups and the availability of the analytical techniques. Aroh and Jensen [27] were pioneers in imposing simultaneously an exponential change in flowrate and temperature ramp for kinetic identification of the Paal–Knorr cyclocondensation reaction, where the outlet concentration profiles were generated through a 10 μL IR flowcell. Expanding on the design of the ramp transient experimentation, Waldron et al. [10] used both intuitively designed and MBDoE approaches for enhancing the estimation of the kinetic parameters of the esterification of benzoic acid with ethanol. They focused on narrow high information zones, utilising HPLC for quantification.

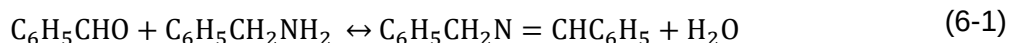
In all documented cases, the use of Plug Flow Reactor (PFR) microreactors has simplified the complexities associated with large transient systems, allowing for the acquisition of more comprehensive datasets in significantly more efficient time frames. Despite the mathematical equivalence of ramping flowrate to a PFR and running a batch reactor [27, 66], intricate calculations of dead volume and dispersion considerations are crucial to prevent erroneous results, as even small deviations from the exact value can lead to unsynchronised data collection, where the acquired data does not represent the real residence times.

To address challenges associated with using a transient PFR, employing a dynamic m-CSTR that operates isothermally involves solving Ordinary Differential Equations (ODEs) for the mass balance of the various reaction components. This approach eliminates the need to predict inlet and outlet times for each fluid element, as the reactor operates at outlet conditions. Furthermore, a m-CSTR equipped with an appropriate window for spectroscopic analysis can be seamlessly integrated with non-invasive techniques like Raman spectroscopy, thus eliminating the dead volume and the time lag between the reaction and the point of analysis. Chapter 6 presents the first exploration of the simplicity inherent in this approach, conducting intuitive ramp transient experiments for both single-variable and multi-variable ramps. The results are compared against each other and juxtaposed with steady-state experiments, offering insights into precise kinetic parameter estimation and time efficiency of this approach.

6.2. Materials and methods

6.2.1. Reaction and experimental setup

The synthesis of *n*-benzylidenebenzylamine in methanol, shown in Equation 6-1, which was introduced in Chapter 5, was employed again.



It was assumed that the reaction rate r_{BAI} can be modelled as a first order reaction with respect to both reactants, benzaldehyde and benzylamine [8], as shown in Equation 6-2.

$$-r_{\text{BAI}} = kC_{\text{BAI}}C_{\text{BAm}} \quad (6-2)$$

Where, C_{BAI} is the concentration of benzaldehyde (mol/m^3), C_{BAm} is the concentration of benzylamine (mol/m^3) and k is the reaction rate constant ($\text{m}^3 \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$), which was expressed in the re-parametrised Arrhenius form with two parameters KP_1 and KP_2 [260], as shown in Equations 6-3, 6-4 and 6-5 respectively.

$$k = Ae^{-\frac{E_\alpha}{RT}} \quad (6-3)$$

$$A = e^{-KP_1 + \frac{KP_2 \cdot b}{R \cdot T_M}} \quad (6-4)$$

$$E_\alpha = KP_2 \cdot b \quad (6-5)$$

Here, T is the reaction temperature (K), b is a scaling factor, and T_M is the reference temperature (K), which in this work, is the average value of the upper and lower temperature limits of the experimental conditions.

In consideration of the already known reaction model, the exploration of inlet concentration was intentionally omitted since it was known beforehand that the variation of the stoichiometric ratio was not a major kinetic factor for the chosen reaction [68]. The focus of the study was narrowed down to the manipulation of two primary experimental design variables: flowrate and temperature. The experimental setup replicated the configuration employed in the steady-state experiments, detailed in Chapter 5, with the exception that the pump for solvent addition was removed. A simplified schematic is provided in Figure 6-1. A stabilisation period, approximately 3 times the calculated residence time equivalent to the baseline flowrate (the initial flowrate prior to the implementation of the ramp), was allowed before measurements were initiated. Raman measurements for transient experiments were directly obtained from within the reaction mixture, assuming the m-CSTR's well-mixed reactor characteristics. A

crucial difference between acquiring steady-state and transient data lies in the development of the analytical methodology. Unlike miniaturised PFR reactors, where a time delay between the measurement and the change of conditions is inherent due to plug flow behaviour [10], the m-CSTR of this system exhibited a simultaneous response to changes that necessitated a synchronised data collection. Consequently, fine-tuning of the Raman spectrometer's sampling frequency was required to ensure that each measurement captured at least one experimental point and that the resulting spectra featured quantifiable peaks. The integration time was set to 300 ms with laser power of 300mW, yielding approximately 1 measurement per second. Continuous background updates were implemented to enhance precision. The LabVIEW code was programmed to update automatically every 3 seconds, resulting in the averaging of three Raman measurements for each transient experimental condition. The system pressure was maintained at 1 barg and the reactants' inlet concentrations were fixed at 2 M.

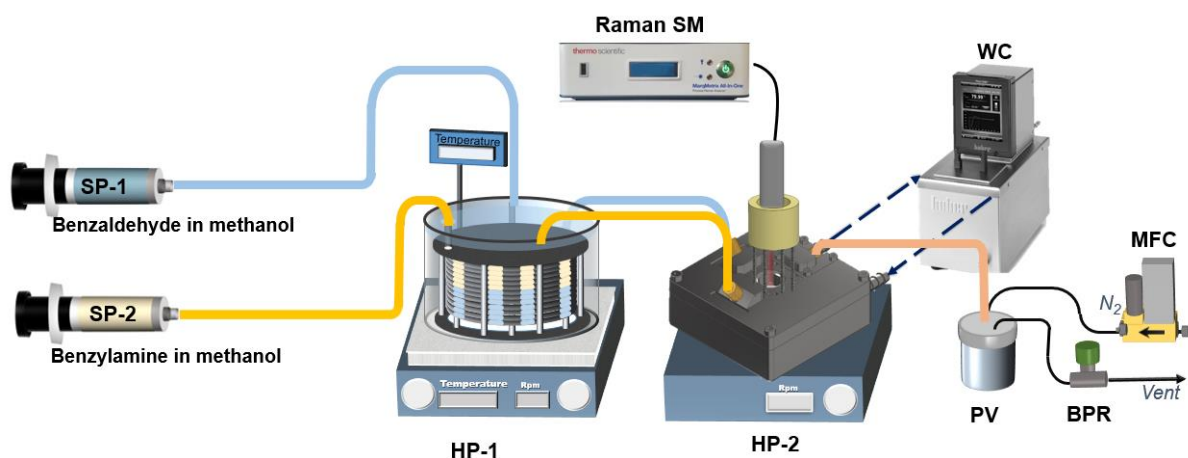


Figure 6-1. Experimental set-up for the kinetic data acquisition of the *n*-benzylidenebenzylamine synthesis under transient conditions. SP: syringe pump, SM: spectrometer, WC: water recirculator, HP: hotplate-stirrer, MFC: mass flow controller, PV: pressure vessel, BPR: back pressure regulator. HP-2 was only used as a stirrer. All temperature, pressure and flow equipment were controlled by LabVIEW.

In accordance with the post-processing procedures outlined in Chapter 5, the determination of reactant and product concentrations involved the area calculation of the characteristic C=O stretching region of benzaldehyde ($1680\text{--}1730\text{ cm}^{-1}$) and the C=N stretching region of *n*-benzylidenebenzylamine ($1630\text{--}1670\text{ cm}^{-1}$). To achieve this, a MATLAB script was implemented, incorporating the airPLS algorithm [449] for baseline correction and matching each Raman spectrum timestamp with the corresponding experimental condition.

Two types of ramp transient experiments were conducted:

- Ramp Q experiments, where only flowrate varied, while temperature remained constant.

- Ramp QT experiments, where both flowrate and temperature underwent systematic ramping.

The primary goal of this study was to utilise the experimental data from a single experiment type to estimate the kinetic parameters KP_1 and KP_2 for the imine formation reaction. This approach facilitated a comparative analysis, aiming to discern the additional insights gained by simultaneously ramping additional control variables. It is noteworthy that for Ramp QT experiments, a single experimental run was adequate for the estimation of kinetic parameters. In contrast, for the Ramp Q experiment, where a constant temperature was maintained, two experiments at different temperatures were necessary to estimate both kinetic parameters.

6.2.2. Modelling transient CSTRs

Since the reactant (benzaldehyde) and the product (*n*-benzylidenebenzylamine) are Raman-active and easy to quantify, the mass balances of both components in a transient, isothermal CSTR of constant volume can be modelled using Equations 6-6 and 6-7, respectively.

$$V_R \frac{d(C_{BAI})}{dt} = Q_0 C_{BAI,0} - Q C_{BAI} - r_{BAI} V_R \quad (6-6)$$

$$V_R \frac{d(C_{Bim})}{dt} = Q_0 C_{Bim,0} - Q C_{Bim} + r_{BAI} V_R \quad (6-7)$$

Where, t is time, V_R is the reactor volume, Q_0 is the inlet volumetric flowrate, Q is the outlet volumetric flowrate and $C_{Bim,0}$, C_{Bim} are the concentrations of *n*-benzylidenebenzylamine in the inlet stream and outlet, respectively. Since there is no *n*-benzylidenebenzylamine in the feed, $C_{Bim,0}=0$, Equations 6-6 and 6-7 can be used for any type of transient experiment including experiments which use ramps, step changes or any other time dependent profile for one of the input control variables. Assuming that no phase changes are taking place, the reaction is in the liquid phase and the densities of the respective reactants and products are comparable, the transient mass balances can be simplified into Equations 6-8 and 6-9.

$$\frac{d(C_{BAI})}{dt} = \frac{C_{BAI,0} - C_{BAI}}{\tau} - r_{BAI} \quad (6-8)$$

$$\frac{d(C_{Bim})}{dt} = \frac{-C_{Bim}}{\tau} + r_{BAI} \quad (6-9)$$

Where τ is the reactor's residence time, $\tau = V_R/Q$.

As in this work the ramp approach was used, a constant ramping rate for each control variable (temperature, α_T and flowrate, α_Q) was specified in the beginning of the experimental cycle. Micro- and milli-scale reactors often operate isothermally at the reaction temperature, whereas the temperature in the syringes from which reagents are pumped through can vary

significantly. As the reactor behaves like an ideal stirred tank, it is expected that the fluid temperature reaches the target value almost immediately upon entry and any heat liberated or absorbed during the chemical reaction (e.g. heat generated due to the laser beam) is rapidly dissipated so that the temperature remains stable throughout the whole reactor. This assumption was validated by continuously monitoring the temperature of the reaction mixture through a type-K thermocouple inserted at the outlet of the reactor. To account for the liquid volume contractions, due to temperature difference from ambient (20 °C) to the reactor temperature, at each transient point, the effective flow rate, Q , takes into consideration the thermal expansion that is quantified by the volumetric coefficient of thermal expansion, α_V . The case of omitting this correction term on the flowrate expression and its effect on the estimation of kinetic parameters was also investigated (Section 6.3.2). Therefore, the flowrate can be described by Equations 6-10 (accounting for the thermal expansion) and 6-11 (not accounting for the thermal expansion) and the temperature by Equation 6-12, respectively. The kinetic parameters reported for each experiment (ramp Q , ramp QT and steady-state) in Section 6.3 were calculated by taking into consideration the thermal expansion of the feed (Equation 6-10).

$$\text{Accounting for thermal expansion: } Q = [1 + \alpha_V \cdot (T - T_0)] \cdot (Q_{\text{initial}} \pm \alpha_Q \cdot t) \quad (6-10)$$

$$\text{Not accounting for thermal expansion: } Q = (Q_{\text{initial}} \pm \alpha_Q \cdot t) \quad (6-11)$$

$$T = T_{\text{initial}} \pm \alpha_T \cdot t \quad (6-12)$$

Here, α_V (1/°C) is the thermal expansion coefficient for methanol (since it is the solvent), α_Q (mL/min²) is the flowrate ramp rate, α_T (°C/min) is the temperature ramp rate, Q_{initial} (mL/min) the initial flowrate of the reactants (baseline flowrate) and T_{initial} (°C) is the initial temperature of the reaction mixture (baseline temperature) and T_0 is the ambient temperature (°C). The mathematical sign chosen depends on the nature of the ramping.

6.2.3. Experimental design

As previously noted, ramp changes can be executed in two directions: from high to low or from low to high values. In the context of intuitively designed experiments, the rationale was to encompass a broad section of the design space. This approach aligns with common strategies in black-box experimental design, where the encouragement of wide spacing is a prevalent practice, particularly in factorial designs [236].

Before the initiation of experiments, several system constraints were carefully taken into consideration:

- Experiment duration: The experiment duration was capped at a maximum of 30 min to ensure practical feasibility, accounting for factors such as the volume of the reactor and the emptying of syringes, and to maintain manageable experimentation timelines.
- Pumping flowrate constraints: The pumping flowrate of each syringe was constrained to not fall below 100 $\mu\text{L}/\text{min}$. This constraint was essential to maintain accuracy of the delivered volume within the specified range.
- Thermoregulator operation: The thermoregulator exhibited a higher heating capacity (1.6-2.1 kW) in comparison to its cooling capacity (0.05-0.2 kW), influencing the choice of ramping directions for temperature changes.

Taking these considerations into account, the experimental design involved the downward ramping of flowrate, paired with the upward ramping of temperature. This approach facilitated screening from low to high residence times, with the added benefit of conserving reaction solution. Furthermore, the data density was increased, as the initial waiting period to reach steady-state for the initial experimental conditions was minimised. In Table 6-1, the chosen ramping rates as well as the initial values of the design variables are reported and the visualisation of them can be found in Figure 6-2.

Table 6-1. Values of the control variables for the ramp experiments.

Ramp	Q_{initial} (mL/min)	α_Q (mL/min ²)	T_{initial} (°C)	α_T (°C/min)	α_V (1/°C) [466]
Flowrate (Q)	4	0.4	15/45	-	0.00149
Flowrate-Temperature (QT)	2	0.05	15	1	

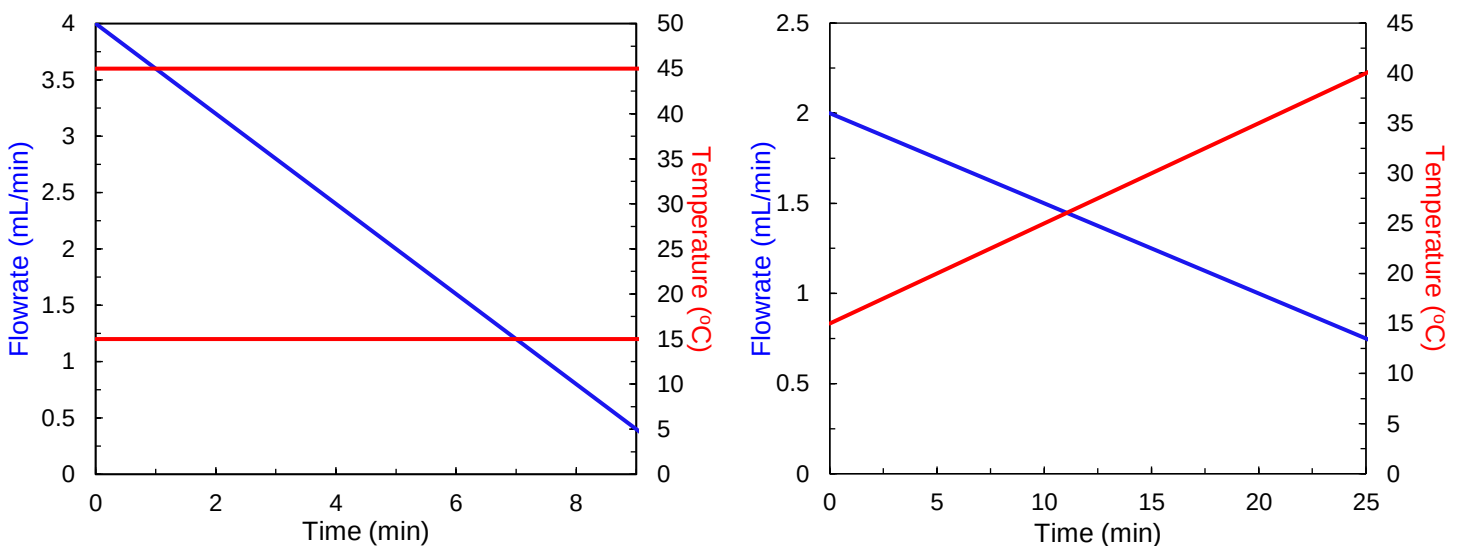


Figure 6-2. Control variable profiles designed by the intuitive method for (a) Ramp Q experiment (in two different temperatures $T=15\text{ }^{\circ}\text{C}$ and $T=45\text{ }^{\circ}\text{C}$) and (b) Ramp QT experiment. Blue lines represent flowrate and red lines represent temperature.

The raw data from the Ramp Q and Ramp QT experiments conducted are shown in Appendix D.

6.2.4. Statistical tools²

Similar to the methodology used in Chapters 4 and 5, Equations 4-11 to 4-17 were used to analyse the parameter estimation in terms of both statistical accuracy (Student's t-test), fitting performance (χ^2 test) and an information analysis was conducted to assess the amount of information obtained from three different types of experiments.

The amount of information is a crucial factor in parameter estimation procedures, as it directly influences the accuracy with which model parameters (θ) can be identified. This analysis was performed by computing a metric derived from the Fisher Information Matrix (FIM), an $N_y \times N_y$ matrix that quantifies the amount of information that can be obtained from a single experiment. For each of the three types of experiments (steady state, transient flowrate and simultaneously transient flowrate and temperature), the FIM ($\mathbf{H}_\theta$) was evaluated using the set of experimental conditions denoted by ϕ , at the values θ of the model parameters:

$$\mathbf{H}_\theta(\theta, \phi) = \left[\mathbf{H}_\theta^0 + \sum_{k=1}^{N_{meas}} \sum_{i=1}^{N_y} \sum_{j=1}^{N_y} \left(\frac{\partial \hat{y}_i(t_k)}{\partial \hat{\theta}_l} \Sigma_{ij} \frac{\partial \hat{y}_j(t_k)^T}{\partial \hat{\theta}_m} \right) \right]_{l,m=1,\dots,N_\theta} \quad (6-13)$$

In Equation 6-13, $\mathbf{H}_\theta$ represents the global information obtained from the experiment while $\mathbf{H}_\theta^0$ is the prior information. $\hat{y}$ refers to the prediction of the i -th concentration at the sampling time t_k . The term in the parenthesis is the product of the sensitivities of each model response to the model parameters. Once the FIM was calculated for all the three types of experiments it was necessary to assess a metric of the information (e.g. trace, determinant or maximum eigenvalue) that can be used to compare the candidate methodologies. In this work the trace of $\mathbf{H}_\theta$ was chosen as an appropriate matrix norm. Based on the information analysis, it was possible to:

- Identify the optimal set of experimental conditions for estimating the model parameters (i.e. the experimental conditions with the highest value of the FIM trace).
- Quantify the amount of information obtainable from one or more experiments.
- Assess the practical identifiability on the parameter estimates.

² The statistical analysis of Chapter 6 was completed with the support of Mr. Andrea Friso from the Department of Chemical Engineering at UCL.

To assess the relative amount of information that can be derived from the estimations obtained using the three different experimental approaches (steady-state, transient flowrate, and transient flowrate+temperature), the Relative Fisher Information (RFI), was also evaluated, based on the FIM definition [261], as shown in Equation 6-14.

$$RFI_{ij} = \frac{\|\mathbf{H}_{ij}\|}{\sum_{i=1}^{N_{exp}} \|\mathbf{H}_{ij}\|} = \frac{\|\mathbf{H}_{ij}\|}{\|\mathbf{H}_j\|} \quad (6-14)$$

where $\|\mathbf{H}_{ij}\|$ represents the Fisher Information Matrix (FIM) for the i -th experiment and the j -th parameter, as computed from Equation 6-14, and $\|\mathbf{H}_j\|$ denotes the total information obtained from the N_{exp} experiments for the identification of the kinetic model parameters. The norm $\|\cdot\|$ can be selected based on various criteria, such as the determinant, the maximum eigenvalue, or the trace of the FIM. In this work, the trace of the FIM has been employed as the chosen norm.

As the information analysis is dependent on the number of experimental data points, a fair comparison between the different tests was guaranteed by using steady state data measured over a longer time. This was achieved by adjusting the sampling methodology and prolonging the duration of each steady-state experiment. After steady state was reached (typically after 3-5 reactor residence times), 5 experimental data points were obtained for each condition, each consisting of an average of 10 Raman spectra. For the steady-state in flow experimentation, the RFI is computed for each experimental condition (i.e. 12 different DoE points) at 3 replicates. For the transient methodologies, the RFI is computed at each measurement point, at 2 or 3 replicates, enabling an assessment of the information profile throughout the course of the experiment.

In Table 6-2, the standard deviation of the measurement error of each of the response variables (concentration of benzaldehyde, C_{BAI} and concentration of n -benzylidenebenzylamine, C_{BIm}), using the method of pooled standard deviation (Equation C-1, Appendix C) [452] for the different ramps is reported.

Table 6-2. Standard deviation of the measurement error of the response variables, concentration of benzaldehyde, C_{BAI} and concentration of n -benzylidenebenzylamine, C_{BIm} .

Ramp	C_{BAI} standard deviation (M)	C_{BIm} standard deviation (M)
Flowrate (Q)	0.0134	0.0273
Flowrate-Temperature (QT)	0.0226	0.0265

6.3. Results and discussion

To investigate the kinetics of the *n*-benzylidene benzylamine synthesis, two different experimental designs have been investigated, as explained in Section 6.2.1.

- Ramp Q experiments
- Ramp QT experiments

The results from these experiments are provided in the following sections in terms of parameter estimation and Fisher Information analysis.

6.3.1. Ramp Q experiments

In Figure 6-3, the measured and predicted concentrations for both the reactant (benzaldehyde) and the product (*n*-benzylidenebenzylamine) are presented for the flowrate ramp from 4 mL/min to 0.5 mL/min under the two extreme temperatures investigated, specifically 15 °C (Figure 6-3a) and 45 °C (Figure 6-3b), respectively. Additionally, the profile of the design variables with time for the ramp Q experiments is displayed (Figure 6-3c). It is important to note that, for visualisation purposes, the plotted measured data points have been substantially reduced from the original dataset, which consisted of 197 experimental data points. From Figure 6-3a and Figure 6-3b, a notable agreement between the model and the experimental data was evident. The re-parameterised kinetic parameters, KP_1 and KP_2 , alongside their corresponding standard deviations and 95% t-values, obtained from the Ramp Q experiments, are presented in Table 6-3.

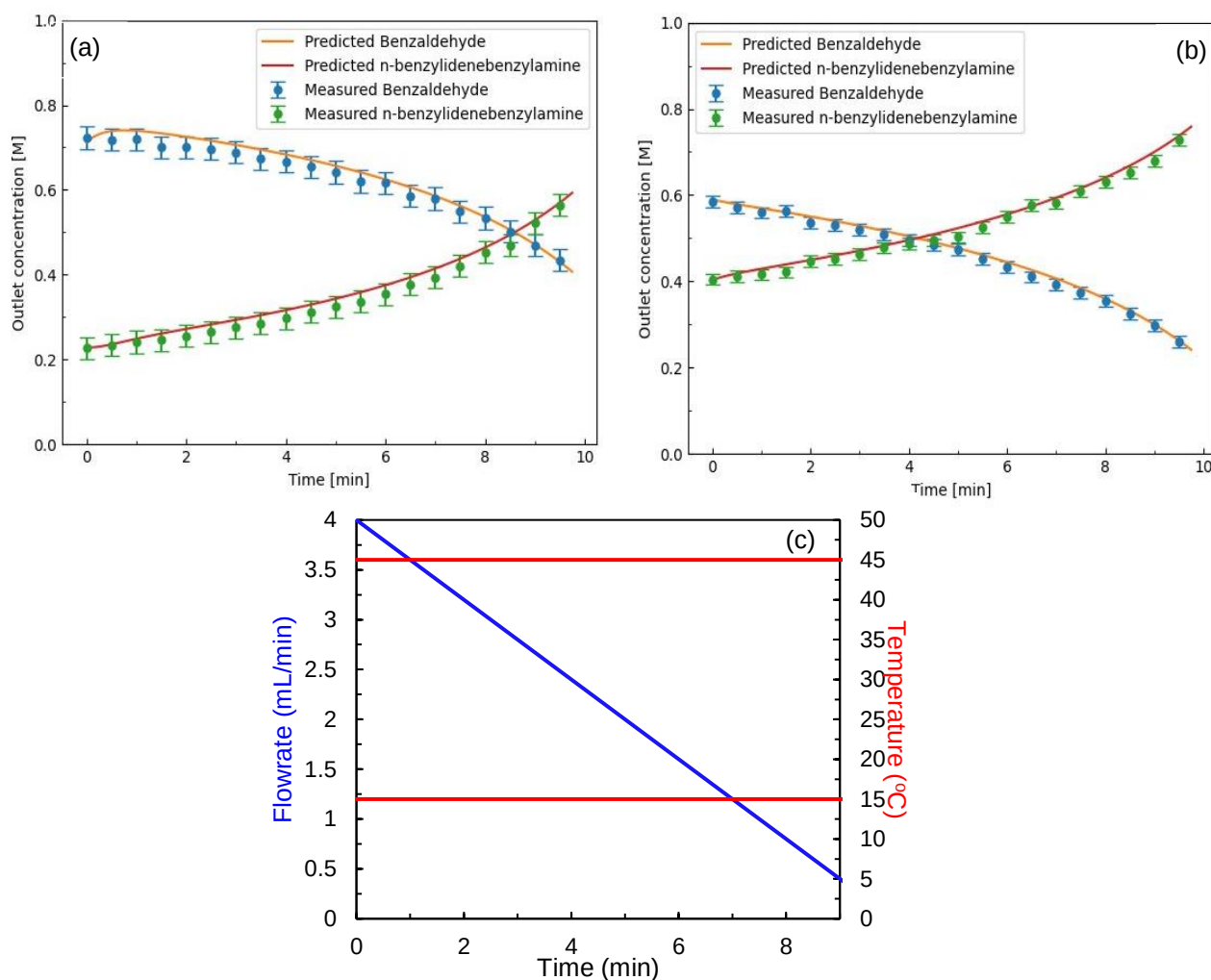


Figure 6-3. Experimentally measured outlet concentrations (a) at 15 °C, (b) 45 °C compared against predicted values based on the parameter estimates and (c) control variable profiles for the Ramp Q experiments. The error bars represent the standard deviation of the measurement error of the response variables.

Table 6-3. Parameter estimation results for the re-parameterised model including the estimated value, standard deviation and 95% t-value.

Parameter	Value	Standard deviation	95% t-value
KP ₁	3.82	0.31	3.50
KP ₂	2.86	7.18	0.54
Reference t-value (95%)	1.65		
χ^2 ($\chi^2_{\text{ref}} = 437.05$)	133.6		

Upon analysing Table 6-3, it was clear that the t-value of parameter KP₂ was lower than the reference t-value, suggesting unsatisfactory estimation of this parameter, as further evidenced by its reported standard deviation. This underscored the limitation in the experimental design, indicating that for the synthesis of *n*-benzylidenebenzylamine, experiments conducted at two different constant temperatures were insufficient to fully isolate the effects of flowrate and temperature. Therefore, while the model appeared to adequately fit the experimental data,

with its χ^2 value being lower than the reference value (χ_{ref}^2), this instance served as a reminder that successful model fitting is inadequate if precise parameter estimation is compromised and that the estimated values of the parameters produced by solely the Q ramp cannot be trusted for model prediction. To improve the precision of the kinetic parameters, an additional temperature point between the extremes was warranted, akin to the approach employed in the steady-state experiments detailed in Chapter 5, or the employment of offline MBD_{oE} to systematically explore the experimental design space instead of an intuitive design, as exemplified in the work of Waldron et al. [10].

6.3.2. Ramp QT experiments

The concentration profiles against time for benzaldehyde and *n*-benzylidenebenzylamine, resulting from the simultaneous ramp-down of flowrate, from 2 mL/min to 0.75 mL/min and ramp-up of temperature from 15 to 40 °C are depicted in . The kinetic parameters obtained from this experiment are detailed in Table 6-4. In contrast to the ramp Q experiments, the second-order kinetics model in the ramp QT not only fitted the experimental data, as the model passes the χ^2 test, but allowed for a precise parameter estimation, as shown by the 95% t-values. To further support this observation, Figure 6-5 compares the correlation matrices of KP_1 and KP_2 for the ramp Q (Figure 6-5a) and for the ramp QT (Figure 6-5b). The values outside the diagonal represent the correlation coefficients of the different parameters (KP_1 and KP_2), ranging between -1 and 1, where values closer to |1| indicate a stronger correlation between the parameters. Examining the correlation between parameters is crucial as high correlation can signal redundancy, meaning that multiple parameters are capturing overlapping information about the system. Moreover, evaluating parameter correlation is essential for robust parameter estimation, as high correlation can suggest ill-conditioned (“sloppy”) models, which can make parameter estimation challenging and less reliable [373]. It is, therefore, evident that for the case of flowrate ramping experiments the correlation between the parameters was strong (> 0.9), whereas for the flowrate and temperature ramping, they were weakly negatively correlated suggesting that temperature ramping can be an effective approach to reduce the correlation among model parameters.

Table 6-4. Parameter estimation results for the re-parameterised model including the estimated value, standard deviation and 95% t-value.

Parameter	Value	Standard deviation	95% t-value
KP_1	3.77	3.90e-5	240.31
KP_2	3.61	4.67e-3	24.49
Reference t-value (95%)	1.65		
χ^2 ($\chi_{\text{ref}}^2 = 1275$)	206.61		

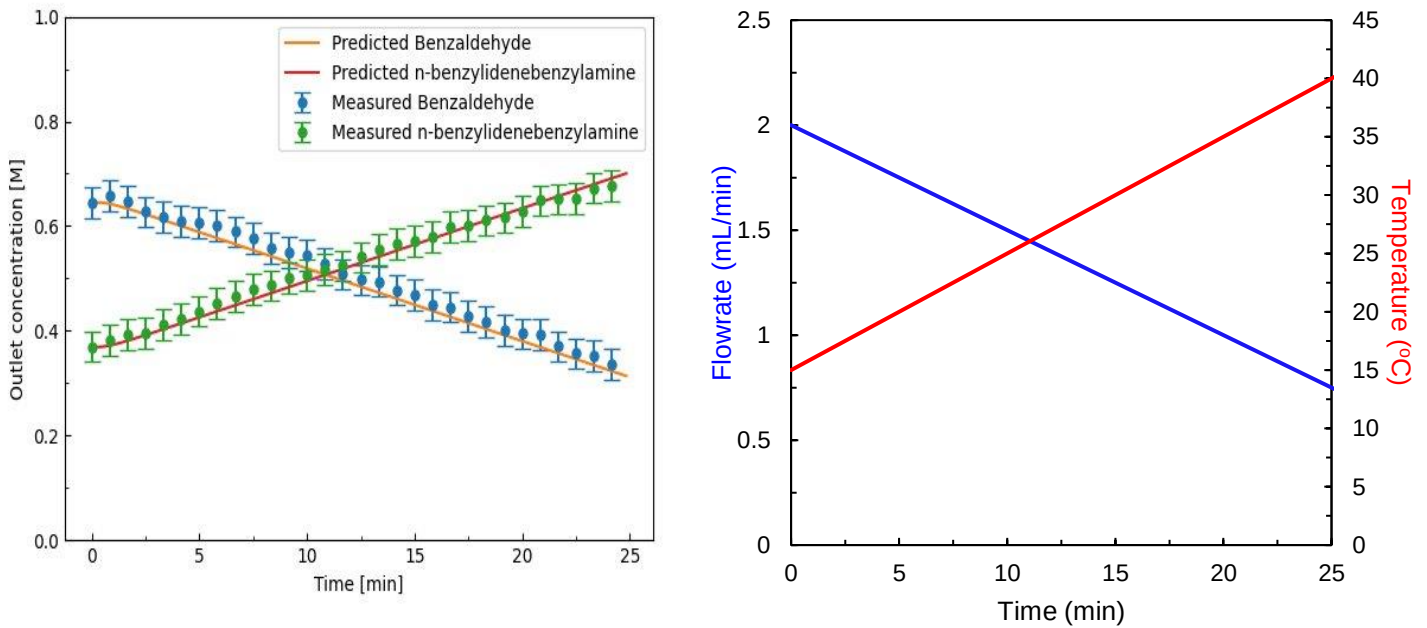


Figure 6-4. (a) Experimentally measured outlet concentrations compared against predicted values based on the parameter estimates and (b) design variables profile for the Ramp QT experiments.

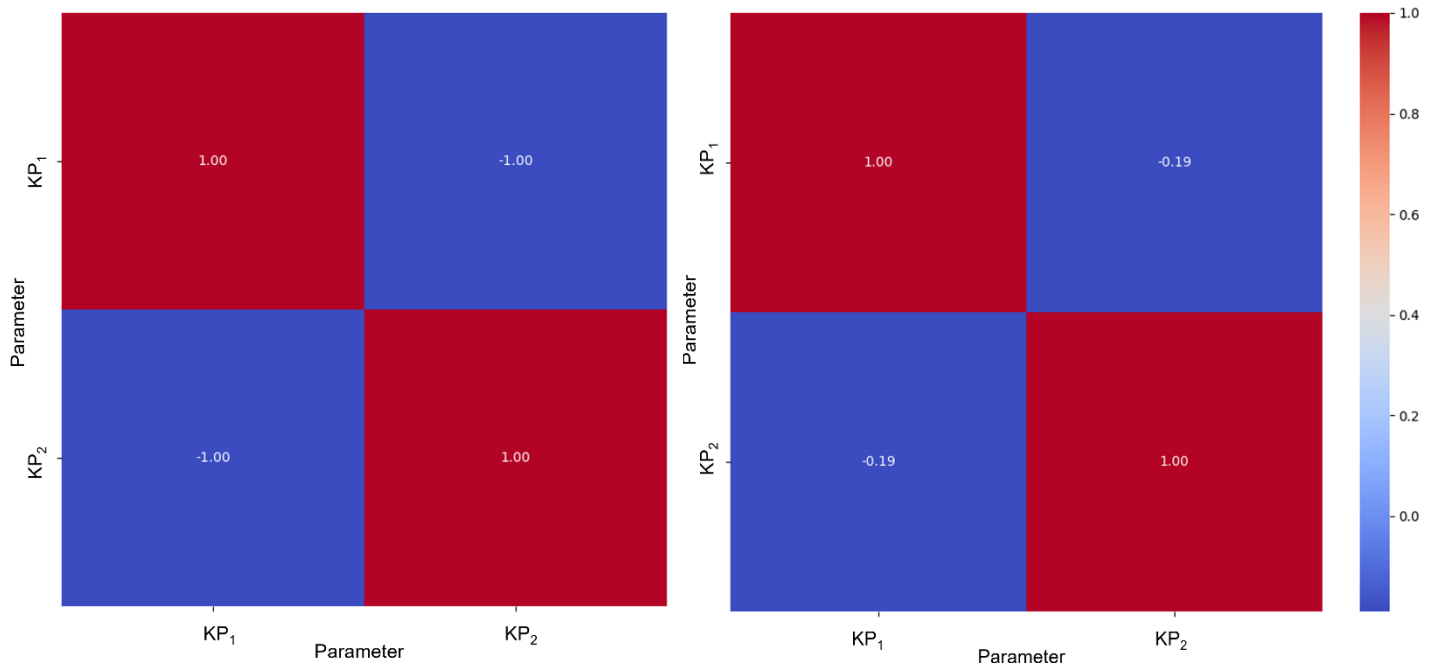


Figure 6-5. Correlation matrix of the model parameters KP_1 and KP_2 generated from the (a) ramp Q and (b) ramp QT experimental data.

6.3.3. Information analysis of different experimental designs

Figure 6-6 displays the FIM for the different experimental ramps (as calculated by Equation 6-14) and compares it with the steady-state experiments (SS), described in Chapter 5. Notably, experiments, where both inlet flowrate and temperature were simultaneously varied, provided the most information, followed by steady-state experiments, while those with only flowrate

changes exhibited a relatively low information content, falling below the information threshold indicated by the black dashed line in Figure 6-6. The threshold represents the minimum amount of information required to satisfy the t-test at 95% confidence level [467, 468].

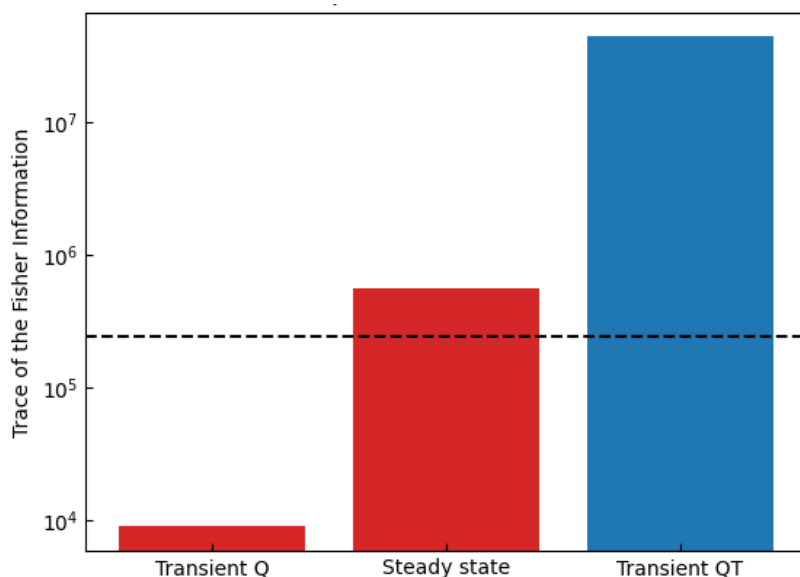


Figure 6-6. Fisher Information analysis for the different experimental techniques employed in this thesis; transient ramps of flowrate and flowrate-temperature and steady-state experiments. The information threshold is indicated by the black broken line.

In Figure 6-8, the Relative Information Fisher (RFI) index for steady-state experimentation is displayed. The RFI is the fraction of information that each experiment (in the case of steady-state) and each experimental point (in the case of ramps) is returning given the parameters KP_1 and KP_2 . RFI enables the ranking of available experiments, highlighting the most informative regions of the design space for parameter identification [261]. From Figure 6-7, which shows the results of the 12 steady-state experiments and their replicates (a total of 180 data points), it is evident that experiment 2 (SS2) yields the highest RFI value, followed by experiment 6 (SS6) and 10 (SS10) (the experimental conditions, including flowrate, temperature, and inlet benzaldehyde concentration, are detailed in Table 5-4). Thus, the experimental region characterised by high reactant concentrations, short residence times (i.e., increased flowrate) and lower temperatures significantly enhanced the estimation of model parameters. Conversely, experiments 7 and 11 (SS7, SS11), described by low flowrate and inlet concentration for both the medium and the high temperature represented poorly informative experiments. Even when repeated, these experiments did not appreciably improve parameter estimation, as they were performed under conditions of low parameter sensitivity, as further supported by the sensitivity plots (based on Equation 4-14) for model parameters KP_1 and KP_2 presented in Figure 6-8a and Figure 6-8b, respectively. Based on Figure 6-8a, the sensitivity magnitude of KP_1 fluctuated between 0.35 and 0.85, exhibiting a recurring

pattern similar to that of Figure 6-8. In the case of KP_2 , as shown in Figure 6-8b, the sensitivity magnitude was lower compared to KP_1 , which impacted the precision of the parameter estimation. The differing patterns in the sensitivity profiles of KP_1 and KP_2 suggested that these parameters influenced the system in distinct ways. In particular, the oscillatory behaviour of KP_2 's sensitivity indicated frequent directional changes in its influence on the system's output and displayed very low sensitivity at 30 °C for every flowrate and inlet concentration investigated, whereas the effect of KP_1 remained consistently positive. Figure 6-9 presents the ranking of experiments for the flowrate ramp based on the Relative Fisher Information (RFI). Two key observations can be made from these experiments: (1) the experiments conducted at 45°C were only marginally more informative than those at 15°C, and (2) the experiment with the highest information content was the one conducted at a total flowrate of 3.6 mL/min (experiment 19), while the remaining experiments exhibited low information content (Transient experimental conditions can be found in Appendix E). These findings align with the results of the parameter estimation, which proved inadequate for precise estimation -particularly for parameter KP_2 - despite passing the chi-square test. In Figure 6-14a, ranged from -0.028 to 0.001, initially starting near zero, decreasing to a minimum at the most informative experiment (experiment 19), and gradually increasing back towards zero. In contrast, the sensitivity profile of KP_2 (Figure 6-14b) followed a similar pattern but with the opposite sign, showing an initial peak, followed by a steady decline. As also observed in the steady-state experiments (Figure 6-8), the sensitivity of the system output to KP_2 remained smaller than that to KP_1 , resulting in the reduced precision of the parameter estimations for KP_2 . Lastly, Figure 6-11 and Figure 6-12 present the RFI and the sensitivity profiles of transient flowrate and temperature. The sensitivity profiles for the transient flowrate and temperature experiments exhibited similarities to those of the transient flowrate alone (Figure 6-10). In Figure 6-12a, the sensitivity of KP_1 reached its peak within the first 20 measurements, after which it remained almost constant for the rest of the data points of the ramp. Similarly, the sensitivity of KP_2 also reached its maximum within the first 20 measurements before declining to zero. This pattern had direct implications for the information content obtained from the transient flowrate and temperature experiments. The relative Fisher information (RFI) plot (Figure 6-11) indicated that most information is captured within the first 120 experiments that correspond to the temperature region of 15 °C – 25 °C and total flowrate range between 1.5 mL/min and 2 mL/min and the uneven distribution (different spikes for different experimental points) can be attributed to the unequal contribution of both model parameters in the RFI.

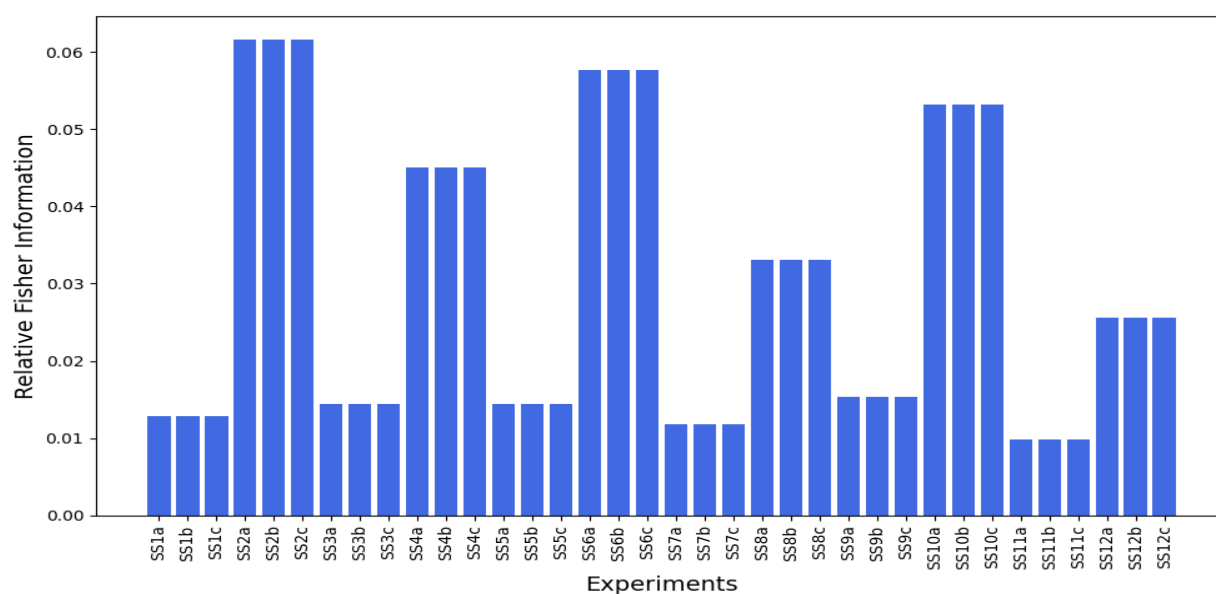


Figure 6-7. RFI evaluation of steady state (SS) experiments. The subscripts a, b, and c refer to the different replicates on consecutive days.

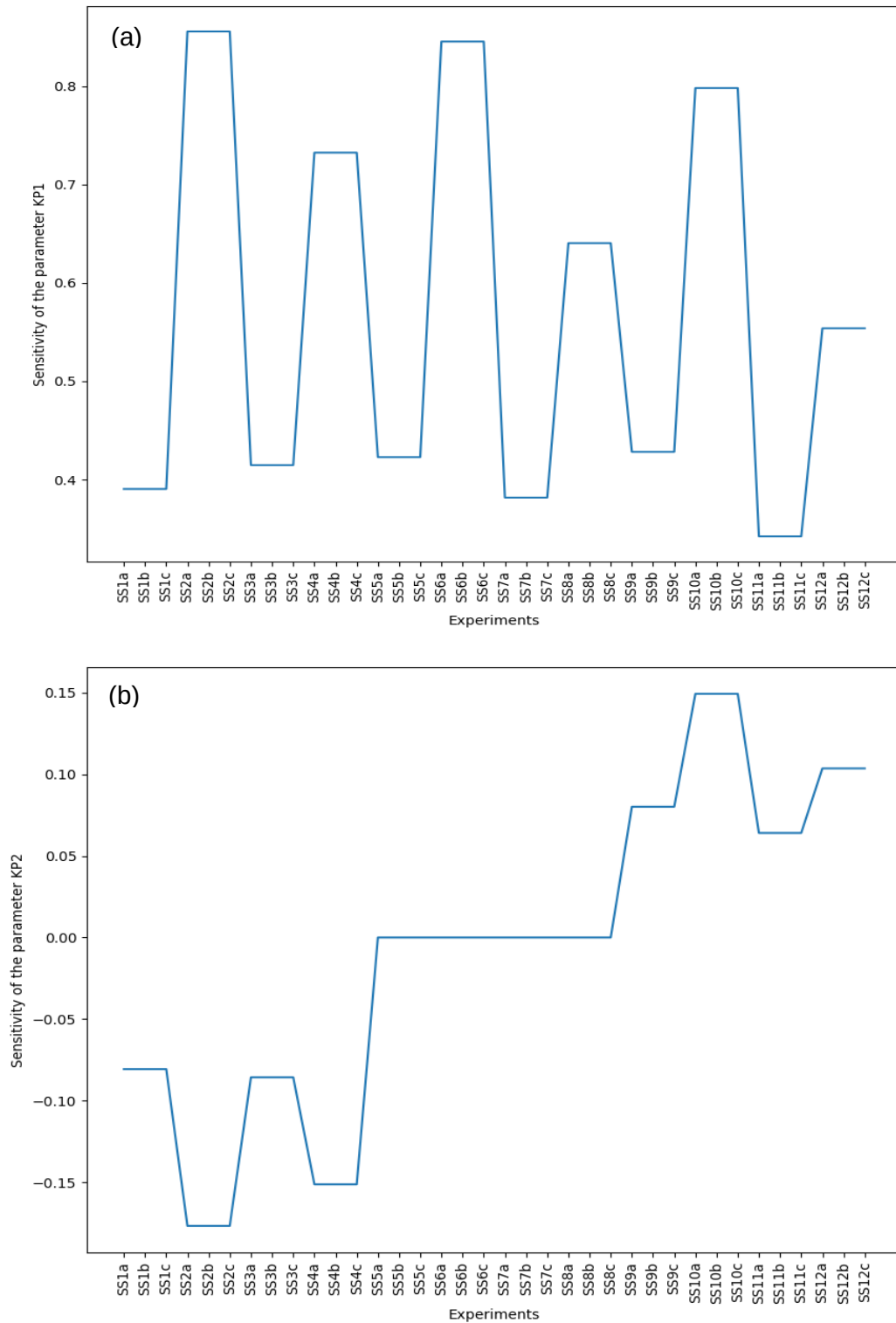


Figure 6-8. Sensitivity profile of (a) KP_1 and (b) KP_2 for the steady state (SS) experiments.

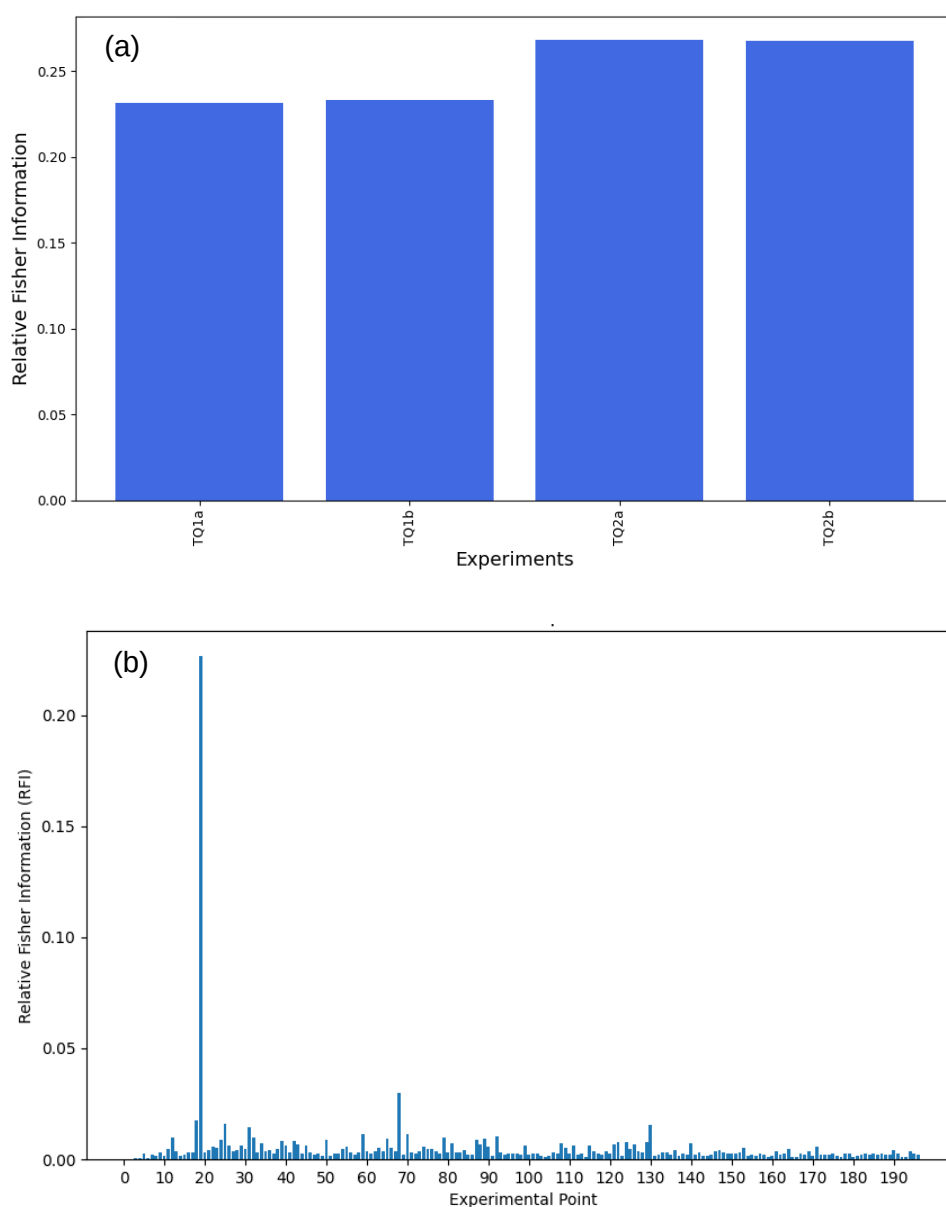


Figure 6-9. RFI evaluation (a) Cumulative of the data points of each transient flowrate (Ramp Q) experiment for the different temperatures investigated (1: 15 °C and 2: 45 °C) and (b) over the course of a Ramp Q experiment for the combination of temperatures. The subscripts a, b refer to the different replicates on consecutive days.

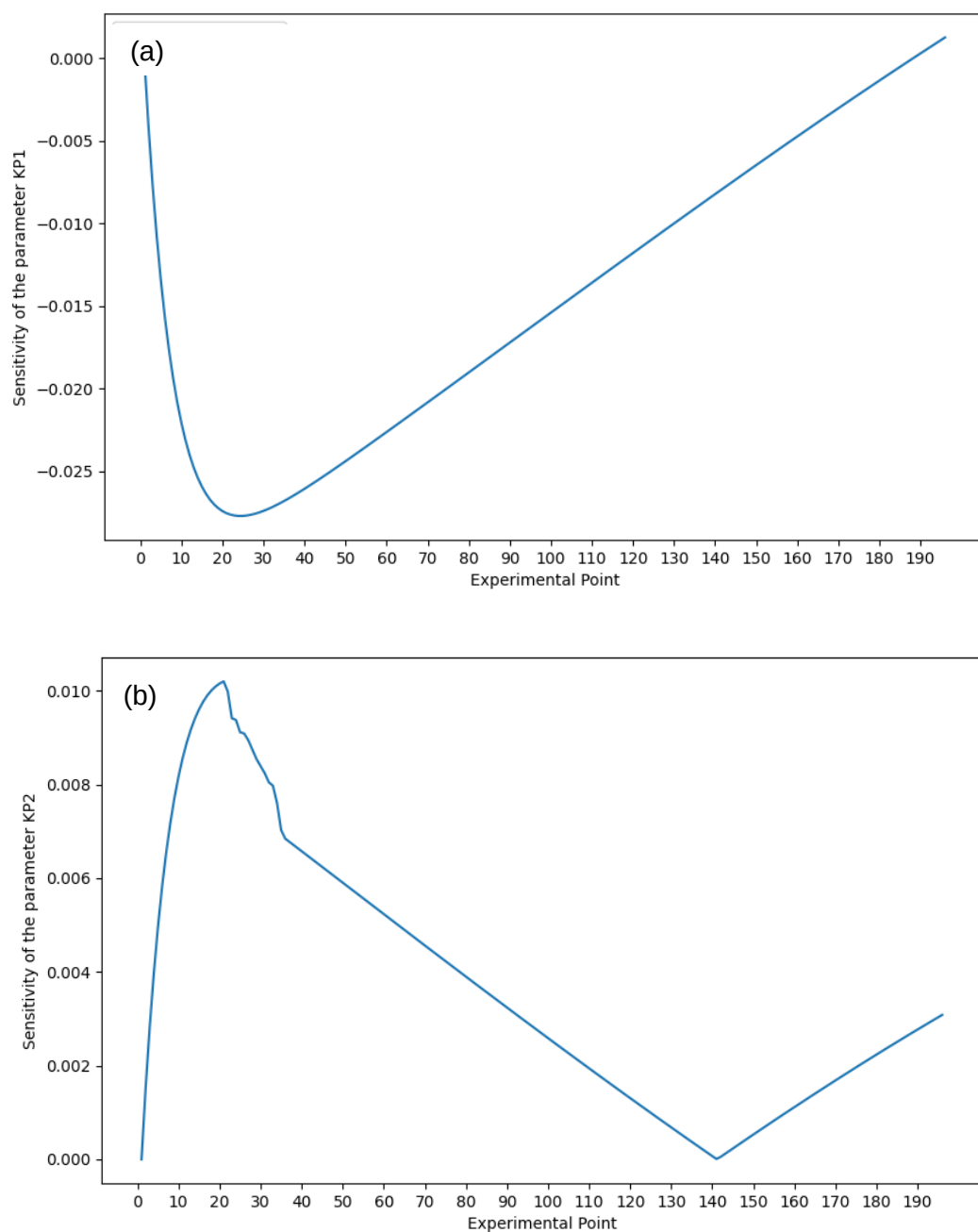


Figure 6-10. Sensitivity profile of (a) KP_1 and (b) KP_2 for the transient flowrate (Ramp Q) experiments.

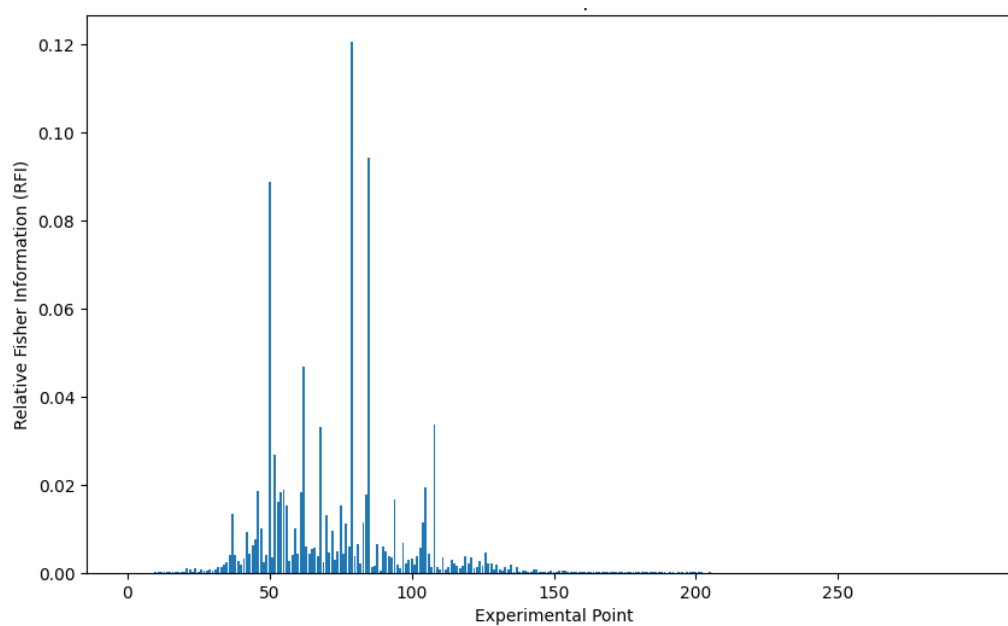


Figure 6-11. RFI evaluation over the course of a flowrate and temperature ramp experiment (Ramp QT).

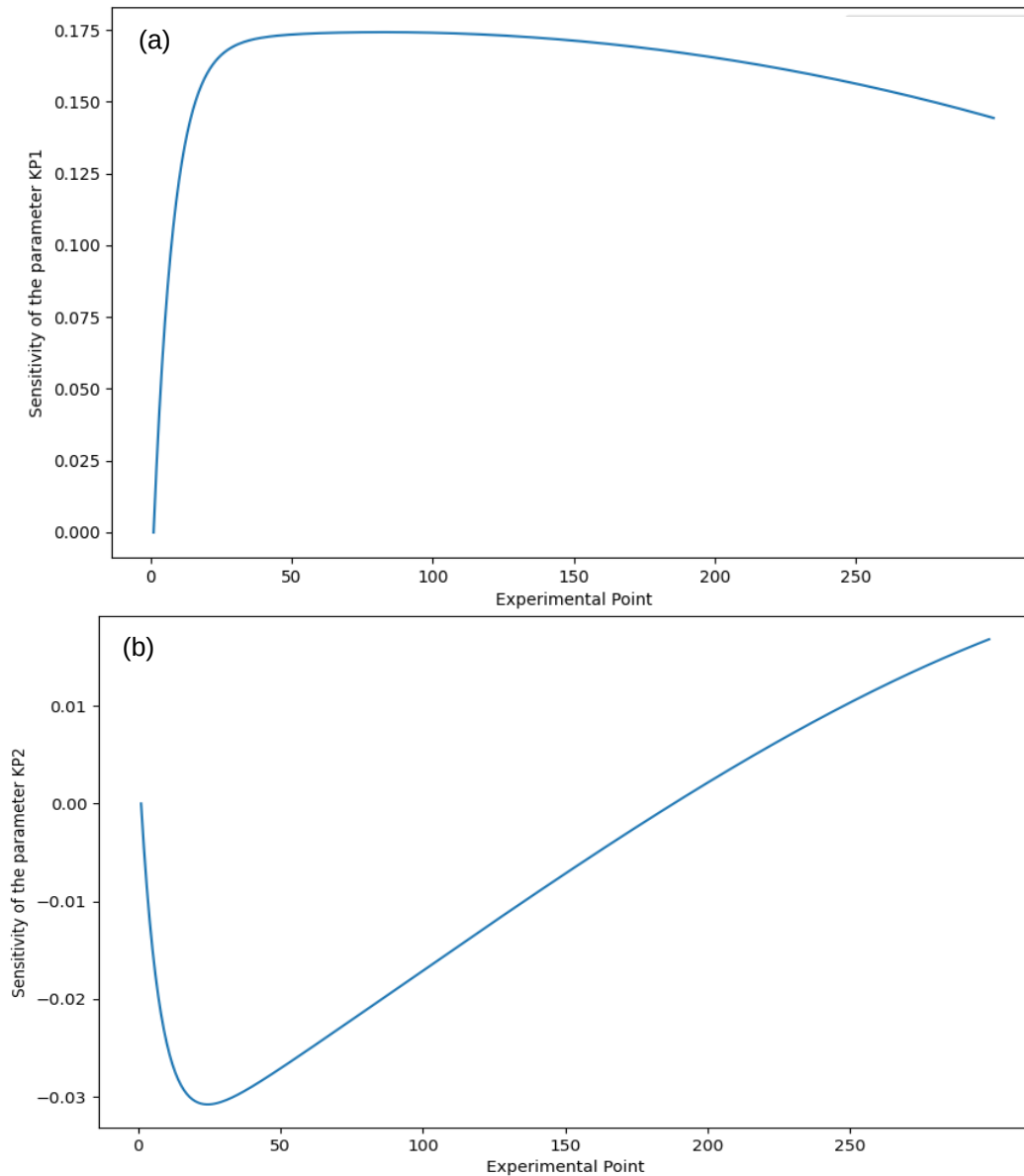


Figure 6-12. Sensitivity profile of (a) KP_1 and (b) KP_2 for the transient flowrate and temperature (Ramp QT) experiments.

To quantify the effect of incorporating the thermal expansion term of the inlet flowrate in the kinetic parameters reported and compare the precision of the parameter estimation, the 95% confidence ellipsoids of the parameter estimates from transient Q, transient QT and SS experiments with (Equation 6-10, denoted as 'TE') and without the thermal expansion correction (Equation 6-11) are shown in Figure 6-13. Figure 6-13 presents four key observations.

1. The confidence ellipsoid of the flowrate ramping experiment appeared as a straight line, indicating significant uncertainty mainly associated with the estimation of KP_2 .
2. There was no overlap between ellipsoids generated by the steady state and transient flowrate and temperature ramping experiments. Considering a correct model and the

adequacy of the variance model used to describe the data, a perfect overlap can only be obtained if there is asymptotic convergence to the best-estimated value. Given that the steady state experiments generated a lower level of information, there cannot yet be asymptotic convergence, as additional steady state experiments would be required.

3. The flowrate and temperature ramping experiment produced the smallest confidence ellipsoid, in comparison with those generated from the campaign of 12 steady state experiments.
4. Lastly, a notable compensation effect between the two estimated parameters KP_1 and KP_2 emerged when considering the thermal expansion term. Omitting this term in flow rate calculations results in temperature-related errors, with a 1% average discrepancy in estimated feed flow rate across a temperature range of 15 to 45°C. This discrepancy corresponds to a -10% to 15% deviation in estimated KP_1 and KP_2 for steady state (SS) experiments, and -1% to 6% for ramp QT experiments, as detailed in Table 6-5. Therefore, the thermal expansion of the inlet was taken into consideration in all estimated kinetic parameters.

Upon re-parameterising the kinetic parameters KP_1 and KP_2 , which exhibited close similarity in value, into the original Arrhenius constants of pre-exponential factor (A) and activation energy (E_a), a significant spread was noted. This divergence is evident in Table 6-6, where the maximum and minimum pre-exponential factor estimates are $1.69 \cdot 10^3$ and $38.30 \cdot 10^3$ ($L \cdot mol^{-1} \cdot s^{-1}$). The disparity in the parameter estimates arose from the exponential transformation between the two parameterisations and the strong correlation between the pre-exponential factor and activation energy. Consequently, to validate the accuracy of using both SS and transient QT experiments in predicting the outlet concentrations of benzaldehyde and *n*-benzylidenebenzylamine, despite the non-overlapping confidence ellipsoids. Experimental measurements were juxtaposed for both experimental designs with simulated concentration profiles, as illustrated in Figure 6-14. Given that the data points presented in Figure 6-14 were obtained from transient experimentation, the steady-state (SS) estimated model failed to adequately capture the transient behaviour of the system. This highlighted a key limitation: steady-state experiments alone did not provide sufficient information for accurately estimating model parameters under dynamic conditions. In contrast, transient experimentation allowed for the acquisition of more detailed information, leading to greater precision in parameter estimation.

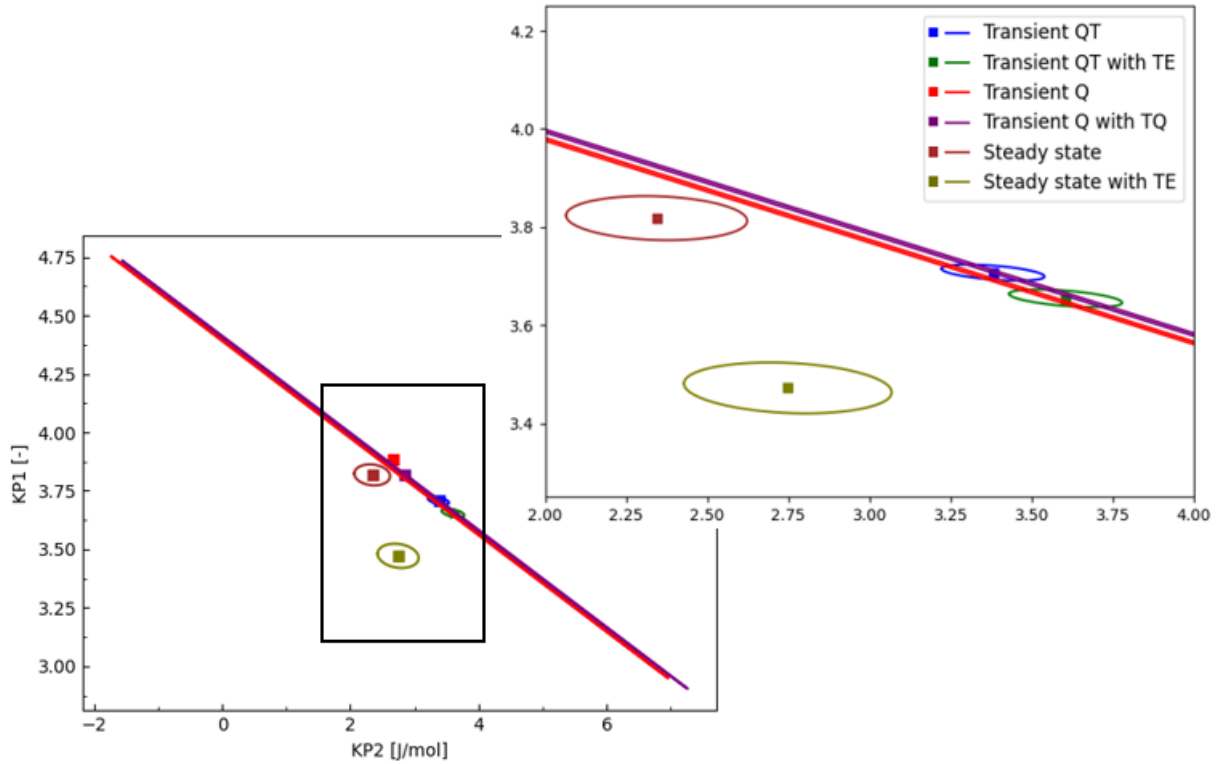


Figure 6-13. 95% Confidence ellipsoids comparing the statistical certainty of the kinetic parameters KP_1 and KP_2 obtained from both steady-state (SS) experiments and transient (Ramp Q and Ramp QT) experiments, with and without the thermal expansion correction (TE).

Table 6-5. Model parameter estimates for Ramp QT and SS experiments and their relative difference when the thermal expansion of the liquid flowrate is accounted for (Equation 6-10) or not (Equation 6-11).

Experiment	Thermal expansion considered?	KP_1	KP_2	Relative difference KP_1	Relative difference KP_2
Ramp QT	Yes	3.77	3.61	-1%	6%
Ramp QT	No	3.82	3.38	-	-
SS, Factorial	Yes	3.47	2.74	-10	15
SS, Factorial	No	3.81	2.34	-	-

Table 6-6. Maximum Likelihood Estimates and 95% confidence intervals for the parameter values KP_1 and KP_2 , and their corresponding values in the original Arrhenius equation, A and E_a for all steady-state and transient QT experiments (taking into account the thermal expansion of the feed), as well as the experiment duration for one experimental cycle.

Experiment	Duration	$KP_1 \pm 95\% \text{ CI}$	$KP_2 \pm 95\% \text{ CI}$	$E_a \text{ (kJ mol}^{-1}\text{)}$	$A \text{ (L mol}^{-1} \text{ s}^{-1}\text{)}$	$k \text{ at } T_{\text{ref}} = 30^\circ\text{C (L mol}^{-1} \text{ s}^{-1}\text{)}$
Ramp QT	25 minutes	$3.77 \pm 7.64\text{e-}5$	$3.61 \pm 9.15\text{e-}3$	36.05	38299.24	0.023
SS, Factorial	4 hours	$3.47 \pm 8.88\text{e-}2$	$2.75 \pm 5.49\text{e-}1$	27.43	1652.67	0.032

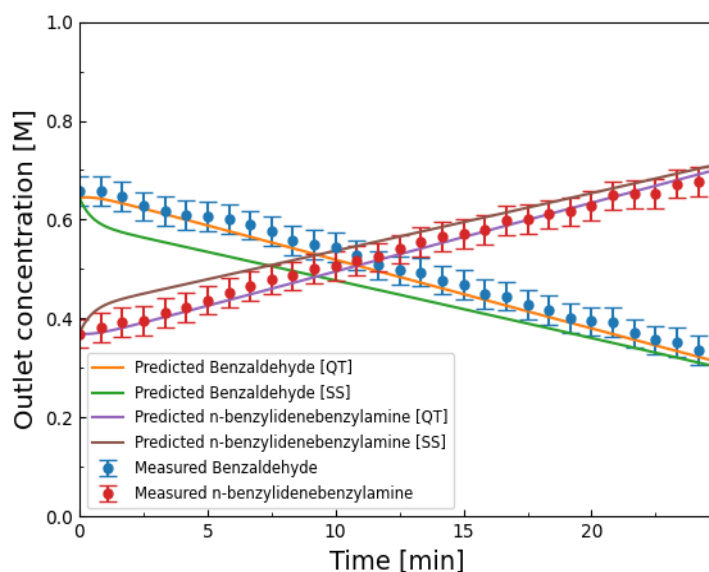


Figure 6-14. Experimentally measured outlet concentrations for the Ramp QT experiments compared against predicted values based on the parameter estimates obtained from Ramp QT and SS experiments, conducted in this work.

The estimated kinetic data of the imine synthesis after performing transient flowrate-temperature experiments were compared with reported values of Fath et al. [67] that conducted similar experiments involving a gradual decrease in flowrate from 2.33 mL/min to 0.37 mL/min by 0.212 mL/min² at three constant temperatures, 15 °C, 35 °C and 45 °C, using an IR Flowcell at the end of a stainless-steel coiled microreactor. Their calculated activation energy, E_a stood 40.1 kJ/mol and the reaction rate coefficient at 25 °C was 0.028 L mol⁻¹ s⁻¹. The findings of this work, revealing an activation energy of 36.1 kJ/mol and a reaction rate coefficient of 0.018 L mol⁻¹ s⁻¹ at 25°C, resonate closely with reported values, thereby reinforcing the reliability and robustness of the transient experimental methodology employed. A summary of the steady-state and transient experimentation methods reported in the literature can be found in Table 6-7.

Furthermore, a key aim of this study was to emphasize the time efficiency gained through transient experiments in comparison to steady-state ones. While each steady-state experimental campaign (12 experiments in total) lasted approximately half a working day to complete (4 hours), transient experiments proved significantly faster. Specifically, one replicate of Ramp Q transient experiments required 20' (comprising 2 experiments conducted at varying temperatures), and the Ramp QT experiments only 25'. Despite the shorter duration (25'), the Ramp QT experiment produced parameter estimates with higher precision levels than experiments lasting roughly ten times longer (steady-state campaigns).

Table 6-7. Comparison of reported kinetic parameters for the synthesis of *n*-benzylidenebenzylamine under steady-state and transient flow conditions.

Reactor setup	Mode	Temperature (°C)	Residence time (min)	$c_{\text{BAI},0}$ (M)	k at 25°C (L mol ⁻¹ s ⁻¹)	E_a (kJ/mol)
Coiled stainless steel microreactor (Fath et al. [67])	Steady-state	15-35	0.2 - 6	2	0.025	39.2
	Transient flowrate ramp	15-35	0.2 - 6	2	0.028	40.1
Oscillating segmented flow reactor (Schulz et al. [68])	Stopped-flow	15-45	/	1	0.036	29.3
m-CSTR (This work)	Steady-state	15-45	1.2-4.6	1	0.026	27.5
	Transient flowrate+temperature ramp	15-40	0.58- 5.8	1	0.018	36.1

6.4. Conclusions

The automated reactor platform (developed in Chapter 5) that comprised a m-CSTR and an inline Raman spectrometer was further extended to conduct transient experiments, yielding kinetic parameters consistent with those obtained from previous steady-state experiments for the synthesis of *n*-benzylidenebenzylamine in methanol. These findings underscored the efficiency of transient experiments in identifying kinetic parameters swiftly, especially when a non-invasive spectroscopic method is employed. When flow rate and temperature were ramped simultaneously, parameter estimates could be acquired in less than 30', in stark contrast to the 4 hours required for one campaign of 12 steady-state experiments. Transient experiments, where both inlet flowrate and temperature were simultaneously varied, provided the most information compared to steady-state experiments and allowed for more precise parameter estimation and a richer mapping of the design space. The study highlighted limitations associated with experimental design, particularly for flowrate ramp experiments that were conducted at two different constant temperatures and proved insufficient to fully isolate the effects of flowrate and temperature, leading to compromised parameter estimation. This pointed out that intuitive designs attempting to cover a wide region of the design space can often result in low-information experiments and imprecise parameter estimates. However, they can serve as a starting point to collect kinetic data and eventually utilise more efficient MBDoE techniques for transient experiment design.

Chapter 7. Conclusions and outlook

7.1. Conclusions

The objective of this thesis was to develop automated platforms tailored for systematically acquiring kinetic information for both heterogeneous (solid-liquid phase) and homogeneous (liquid phase) systems. The core of this research involved the fabrication, as well as experimental and computational characterisation in terms of hydrodynamic behaviour, mixing and mass transfer of miniaturised reactors, with focus on relatively unexplored reactor concepts, such as Single Pellet String Reactors (SPSRs) and miniaturised CSTRs (m-CSTRs) for reaction kinetics. These reactors were integrated with online High-Performance Liquid Chromatography (HPLC) and inline Raman spectroscopy in a plug-and-play mode.

The flexibility of the automated, LabVIEW-controlled system to accommodate different reactor types and analytical techniques and swiftly transition to different experimental conditions with minor adjustments streamlined the experiment setup and execution. This demonstrated that the time saved from automating the experiments outweighed the time spent on developing the platforms. A general methodology for conducting efficient kinetic studies was developed to maximise the benefit obtained from the automated reactor. This general methodology included aspects of traditional DoE for situations with limited prior knowledge and practical identifiability tests to prevent the wastage of resources on non-identifiable models. To conclude upon a kinetic model and its relative kinetic parameters, the experimental data underwent evaluation for model discrimination and precise parameter estimation.

Chapter 3 presented a comprehensive exploration of SPSRs' hydrodynamics and liquid-to-solid mass transfer using a CFD model developed in COMSOL Multiphysics® v. 6.1 to investigate the hydrodynamics and liquid-to-solid mass transfer in SPSRs. The investigated SPSRs composed of cylindrical channels packed with spherical particles averaging 947 μm in diameter, with aspect ratios ranging from 1.06 to 1.68, operating under laminar flow conditions. The model's accuracy was verified against experimental data obtained from the copper dissolution technique. Two approaches were employed to post-process the model results and calculate the external mass transfer coefficient. The first approach adopted a macroscopic method relying on established mass balance equations for packed beds, to estimate an average mass transfer coefficient across the bed. The second approach was microscopic, allowing estimation of local mass transfer around the spheres, followed by averaging along the reactor length. Comparison of the two methodologies revealed limitations in the macroscopic treatment, particularly for composite reactors with small aspect ratios, where non-uniformity in momentum and mass transfer, induced by wall effects, led to an overestimation of mass transfer rates. Consequently, new correlations based on the

microscopic approach were formulated to estimate the liquid-to-solid mass transfer coefficient, elucidating the interplay between hydrodynamics, mass transfer, and reaction kinetics in SPSRs. These correlations highlighted the aspect ratio's influence on enhancing mass transfer, underscoring the potential of SPSRs to acquire intrinsic kinetics without external mass transfer limitations, thus offering a valuable alternative to cumbersome experimental procedures for assessing mass transfer in such systems.

The hydrodynamic study and mass transfer correlations developed in Chapter 3 highlighted the potential of SPSRs for catalyst screening under industrial conditions, particularly for identifying kinetics of heterogeneously catalysed reactions in flow, free from external mass transfer limitations. With a focus on the increasing interest in alkyl derivatives of levulinic acid as green fuels, particularly ethyl levulinate, Chapter 4 aimed at systematically screening a diverse range of models to obtain kinetics for the continuous esterification reaction of LA with ethanol over commercially available Amberlyst-15 particles. Starting from simple reaction rate expressions, the study progressed towards the formulation of mechanistic models described by equations containing numerous kinetic parameters. Recognising that increasing model complexity heightened the risk of unidentifiable parameters in the experimental design space, an automated platform in LabVIEW that incorporated online HPLC analysis, and advanced algorithms for model identification, selection, and parameter estimation were developed. Given the macroporous structure of the catalyst and the presence of internal mass transfer resistances due to the commercially available sizes, the reported kinetic models reflected apparent kinetics. Ultimately, a Langmuir-Hinshelwood-Hougen-Watson model and an Eley-Rideal model, incorporating a temperature-dependent term for water adsorption equilibrium, emerged as the most suitable kinetic models for EL production from LA in the investigated design space. Both models revealed water's strong tendency to bind to catalytic sites, thereby inhibiting the reaction. Given the similarity between the final reaction rate expressions, further discrimination in the platform was not feasible.

Chapter 5 of this thesis delved into exploring the potential of combining non-invasive spectroscopy with continuous systems to monitor reactions in real-time and acquire precise kinetic parameter estimates. This was exemplified through the fabrication of a miniaturised CSTR unit that was incorporated into the LabVIEW interface, developed in Chapter 4, with minimal modifications. The m-CSTR was designed for plug-and-play functionality and was equipped with an inline Raman spectrometer probe. The reactor assembly featured a stainless-steel reactor chamber with a quartz glass window, a custom-made PTFE impeller and an integrated heating jacket, enabling reaction control below room temperature. Notably, the reactor's adaptable window selection and easy replacement mechanism made it suitable

for various spectroscopic techniques beyond Raman spectroscopy. Furthermore, the custom-designed impeller ensured nearly-ideal CSTR behaviour when one and both inlets of the reactor were used, as demonstrated by the experimental RTD analysis. Employing the Villiermaux-Dushman methodology to evaluate micromixing efficiency showcased better performance of the custom-made impeller compared to a conventional cross-shaped stirring bar of similar dimensions. This highlighted the significance of innovative reactor design in optimising mixing efficiency and reactor performance in continuous flow systems. Through COMSOL Multiphysics® v. 6.1. simulations, the turbulent velocity profile was thoroughly examined. The study revealed that the custom-made impeller functioned as an axial impeller, generating swirling flow patterns that dominated the flow field across a wide range of inlet flow rates, with vortices extending throughout the reactor depth. As the main focus was the employment of the reactor for kinetics in flow, the kinetic parameters of the second order n -benzylidenebenzylamine synthesis from benzaldehyde and benzylamine in methanol were determined. Using Raman spectral data obtained directly from the inside of the m-CSTR, the concentrations of the reaction species were quantified after being processed with a simple but efficient baseline correction methodology. The reactor's capability to function simultaneously as a stirred flow cell enhanced its utility for monitoring reactions involving solid formation or suspension, such as crystallisation reactions. This multifunctionality underscored the versatility and broad applicability of the developed reactor system.

Although transient experimentation for rapidly acquiring reaction kinetics in milli fluidic PFR reactors was reported for the first time over a decade ago, the intricate calculations of dead volume and dispersion considerations to prevent unsynchronised data collection continue to pose challenges in automated setups. Leveraging the miniaturised CSTR developed in Chapter 5, Chapter 6 investigated its dynamic isothermal operation coupled with Raman spectroscopy, conducting intuitive ramp transient experiments for both single-variable and multi-variable ramps. By ramping down the flow rate at two different constant temperatures, it was observed that although a second-order reaction rate model appeared to adequately fit the experimental data, precise parameter estimation was compromised. This highlighted that intuitive designs aiming to cover a wide region of the design space often result in low-information experiments and imprecise parameter estimates. Transient experiments, where both inlet flow rate and temperature were simultaneously varied, provided the most information compared to steady-state and transient flow rate experiments, enabling more precise parameter estimation and a richer mapping of the design space. In terms of time efficiency, when flow rate and temperature were ramped simultaneously, parameter estimates could be acquired in less than 30 minutes, sharply contrasting with the 4 hours required for one campaign of 12 steady-state experiments.

7.2. Future work

7.2.1. Improvements for the model identification of the esterification of LA with ethanol in flow over Amberlyst-15

In Chapter 4, the esterification of levulinic acid with ethanol in the presence of Amberlyst-15 was conducted using a continuous SPSR, which was part of an automated platform controlled by LabVIEW. Due to the macroreticular structure of the catalyst and the fact that less than 1% of the commercial catalyst particles were smaller than 300 μm , it was not possible to exclude internal mass transfer resistances. As a result, the kinetic models presented reflected apparent kinetics. To accurately report intrinsic kinetics, it is essential to quantify internal mass transfer, typically represented by the Thiele modulus in the reaction kinetic expression [90]. Since the Weisz-Prater criterion relies on the premise of a first-order reaction, its applicability is uncertain for kinetic models like the LHHW and ER discussed in this study.

Calculating internal mass transfer resistances involves using finite difference methods to numerically solve the governing differential mass and energy balance equations within a single porous particle (diffusion-reaction equations) [397], as described by Russo et al. [346, 366] for similar systems. However, applying this methodology would necessitate batch experimentation beforehand to assume a constant bulk concentration around the particles. To numerically solve the diffusion-reaction equations along the length of a SPSR, the estimation of concentration at each point would be required. One approach could involve assuming a bulk concentration equal to either the inlet or outlet concentration for the first and last particle, respectively. It is important to note that although Amberlyst-15 is a commercial catalyst with the highest activity among both zeolites and non-zeolitic materials for the esterification of LA [335], it presents mass transfer constraints for this reaction in batch or flow experiments. Therefore, reaction kinetics for the synthesis of EL by LA in alternative catalysts, with less complicated networks of porosity that are easier to use in industrial scale-up, might need to be considered.

Additionally, the non-ideality of the reaction mixture is a crucial factor to consider. Water, the main reaction product, and ethanol, the solvent, form an azeotrope, which complicates the analysis [469]. A more precise approach would involve considering activities rather than concentrations, although this may compromise the practicality of the study. For the experimental design space of Chapter 4, activity coefficients, γ , and the corresponding activities, a , for the components of the reaction mixture were calculated using the commercial process simulation software Aspen Plus®, based on the UNIFAC thermodynamic model with Dortmund Data Bank parameters [470], as shown in Table F-1 and Table F-2 of Appendix F. From Table F-1 and Table F-2, it can be deduced that the activity coefficients for LA and EL

are slightly higher than 1, indicating a small deviation from ideal behaviour. However, the same does not apply for water, which has an activity coefficient larger than 2. Considering these results and the availability of existing Python libraries such as Phasepy [471], future work could focus on incorporating a thermodynamic model into the statistical analysis, thereby also enhancing the capabilities of MBDoE for model discrimination and parameter estimation.

7.2.2. Development of the miniaturised CSTR platform for multi-phase reactions with various spectroscopic techniques

The m-CSTR, introduced in Chapters 5 and 6, has emerged as a valuable tool for conducting rapid and reliable kinetic studies of liquid-phase reactions that serve as a preliminary study for proof of concept in both steady-state and transient modes. Leveraging the reactor's ability to handle solids, the miniaturised CSTR can be repurposed as a stirred flow-cell for investigating reaction kinetics in solid-producing reactions or those involving heterogeneous catalysts (as briefly explored in Appendix C). However, in both scenarios, the suspension of solid products or catalysts inside the reactor chamber may lead to reduction in the intensity of the acquired Raman signal, posing challenges for component quantification via peak integration.

A potential strategy for addressing this issue, particularly in the case of heterogeneous catalysts, involves optimizing the design of the impeller. A proposed avenue for future research is the transformation of the m-CSTR into a spinning basket reactor, inspired by the Carberry spinning basket reactor [472], where each arm of the custom-made impeller contains the tested catalyst [473, 474]. Additionally, another consideration is the design and 3D-printing of catalytically-active impellers [475], wherein the catalyst is not supported inside the arm by a fine mesh, but is impregnated in the stirring device itself. Both designs would allow for the catalyst to be removed from the reaction once completed, thereby simplifying isolation and purification processes while also mitigating the effects of turbidity in the Raman spectrum [414].

Moreover, given the successful demonstration of m-CSTRs for multiphasic systems [75], the m-CSTR unit developed in this work can also be used for acquisition of inline reaction kinetics using Raman involving gas-liquid systems. Although the introduction of gas is expected to result in lower peak intensity due to the lack of signal from gas bubbles, strategic positioning of the probe and the reactor (e.g., aligning them in the direction of flow where gas bubbles rise faster than the liquid) can ensure that the laser focuses on the liquid phase, yielding valuable concentration data.

In this work, Raman measurements were conducted in situ, but the Raman spectrometer was not controlled by LabVIEW. For transient experiments, where matching acquired Raman signals with changes in flow rate or temperature was crucial, spectrum recording necessitated

the presence of the experimentalist to track the initial and final experimental conditions, along with the development of a post-processing MATLAB script. To streamline experimental procedures and enhance efficiency, it is proposed to develop an interface between LabVIEW and the Raman spectrometer probe. Such integration would not only facilitate real-time data acquisition but also enable the utilization of acquired data as input for embedded MBDoE algorithms within the LabVIEW platform. These algorithms aim to minimise the number of experiments required for identifying the correct model structure and precisely estimating model parameters.

Lastly, another suggestion for further expanding the capabilities of the m-CSTR for acquiring kinetics of liquid-phase reactions is coupling the reactor with other in-situ spectroscopic techniques and specifically IR microreflectance, a concept briefly explored in this thesis but not fully realised (Appendix E). While this integration may present challenges related to the material of the window, the nature of the reaction components (e.g. aqueous solutions are avoided due to the strong absorbance of water in the IR region), as well as efficient stirring of the chamber to ensure that the reflective surface, where the incident IR beam is focused, is representative of the entire reaction mixture, it presents a novel opportunity for extending IR spectroscopic techniques beyond ATR mode. Such an endeavour would require collaboration among multiple scientists, including a reactor design engineer, an optical engineer and a spectroscopy specialist.

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Appendix A. Modelling of hydrodynamics and liquid-to-particle mass transfer in a Single Pellet String Reactor (SI from Chapter 3)

A1. Mesh details and introduction of gaps

Due to the intricate nature of the reactor's geometry, the mesh generated contained elements of lower quality in the areas of contact points between the solids (particle-particle, particle-wall), where the elements become very skewed, meaning that some of their surfaces are much larger than others within the one tetrahedron. This skewed mesh around the contact points did not seem to create any problems for laminar solutions concerning model convergence. Details of the mesh in these areas are presented in Figure A-1.

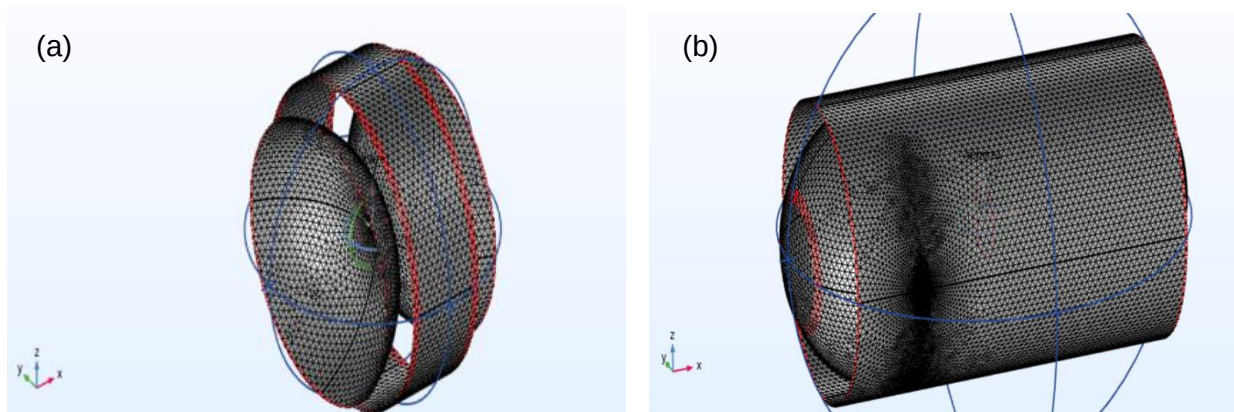


Figure A-1. Details of the mesh at the contact points of the solids (a) between spheres and (b) between spheres and the wall.

However, these elements can be eliminated following the approaches of the so-called 'shrink' factor or 'near-miss' model introduced by Calis et al. [290] and Nijemeisland and Dixon [300] respectively, where all particles are shrunk by 1% of the diameter after the initial definition of the bed. In other words, the positions of all particles in the packed bed were calculated based on a certain particle diameter d_p , but the particles defined in the CFD domain have a diameter of only $0.99d_p$. As a result, the packings contain no points of contact. A comparison of the geometries with and without contact points can be found in Figure A-2a and Figure A-2b, respectively.

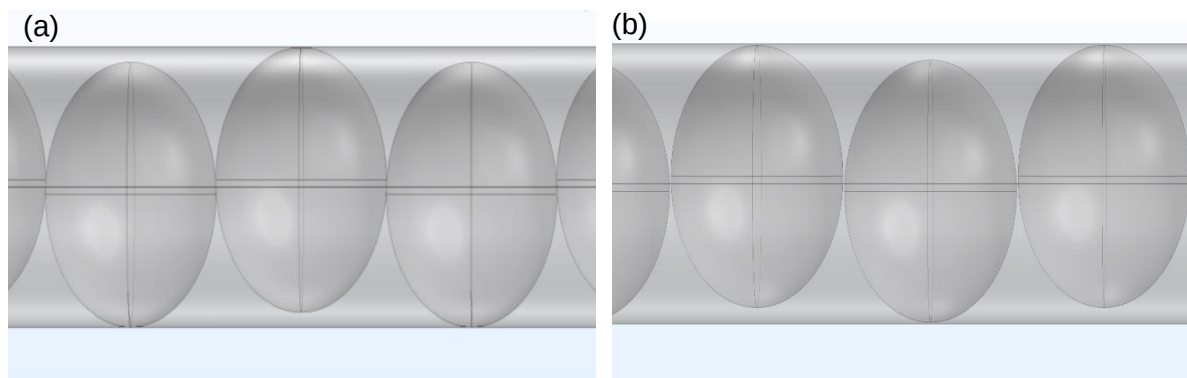


Figure A-2. Comparison of a reactor geometry with (a) contact points (b) no contact points.

The two approaches were compared by evaluating the relative differences in the average fluid velocity and average bulk concentration on planes crossing the centre of two random spheres (2nd and 7th copper particle) and the contact point between sequential spheres, as illustrated in Figure A-3. The results presented in Figure A-4 revealed that the bulk concentration for a shrink factor of 1% is representative (<5% relative error) for the full solid-solid contact. Nevertheless, for the velocity magnitude the relative error lies between 7 and 14% for the contact points of the spheres and the contact points of the sphere with the wall. These results are in line with the observations of Nijemeisland and Dixon [300]. To ensure that the flow profile was described properly, the approach which included the contact points was followed.

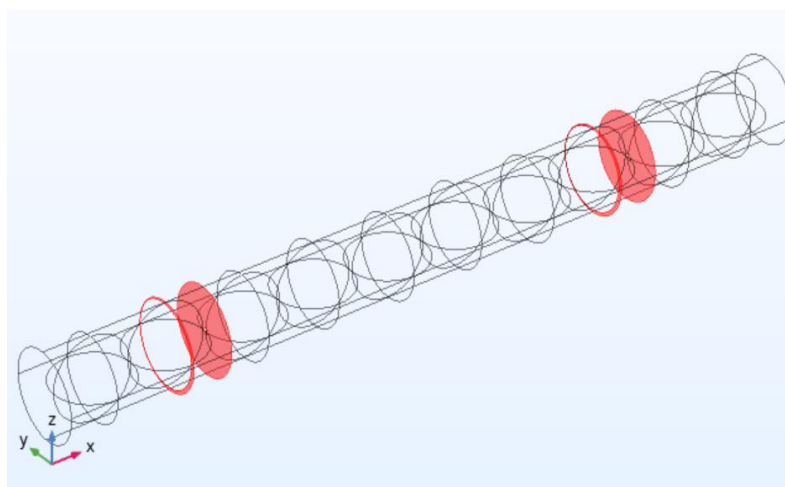


Figure A-3. Illustration of the points evaluated in the SPSR geometry for the final determination of the mesh.

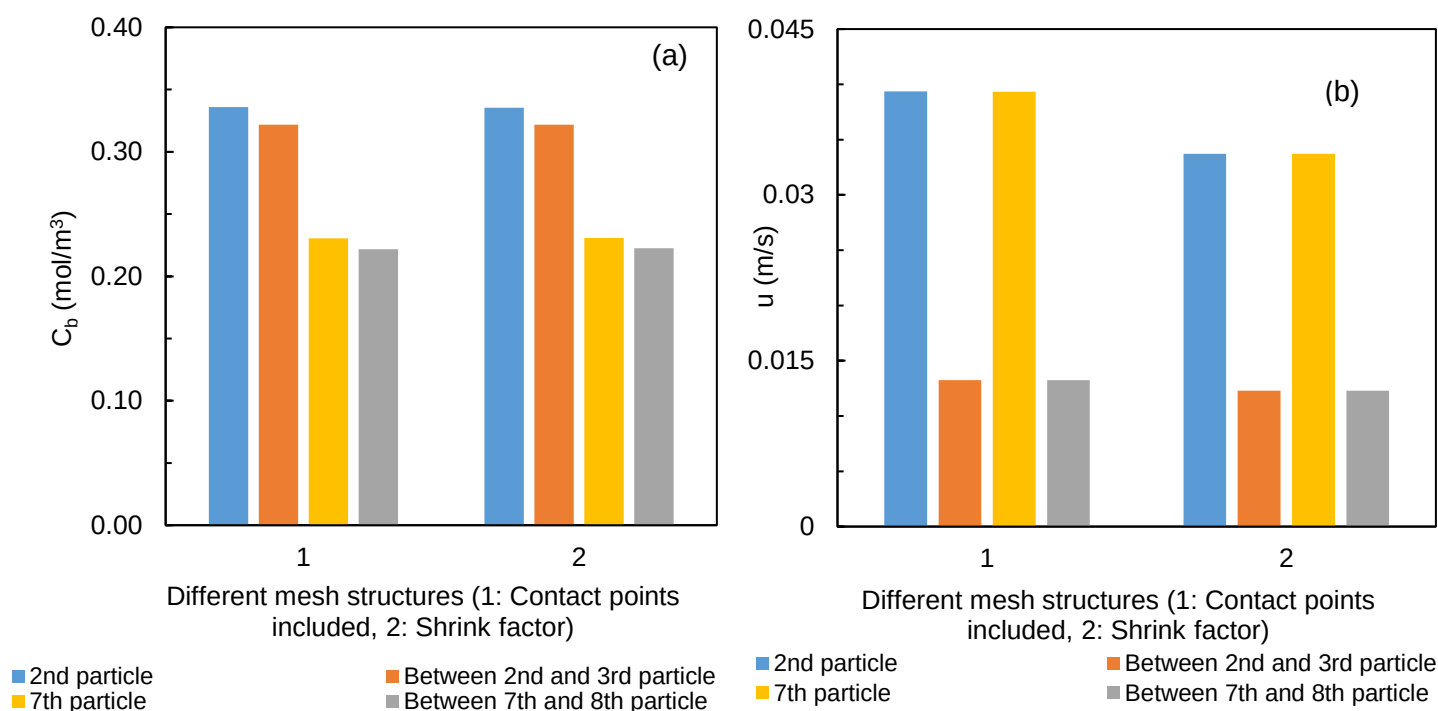


Figure A-4. (a) Concentration of dichromate anions and (b) Velocity histograms for comparison of the different gap sizes along the length of the reactor bed.

A2. Calculation of model parameters

The average porosity, ε , of the SPSRs with spherical particles, considering the aspect ratio (δ) and incorporating the influence of the ordered packing adjacent to the wall, was calculated based on the correlation proposed by Dixon et al. [301], as shown in Equation A-1.

$$\text{For } \delta \leq 1.87, \quad \varepsilon = 1 - 0.667 \left(\frac{1}{\delta} \right)^3 + \left(\frac{2}{\delta} - 1 \right)^{-0.5} \quad (\text{A-1})$$

Additionally, the weighting factor, f_w , introduced to the surface of the confining wall for the calculation of the modified equivalent diameter, d_h , (Equation 3-9) was calculated based on the empirical equation proposed by Fernengel et al. [302] (Equation A-2).

$$\text{For } 1.125 \leq \delta \leq 1.75, \quad f_w = 0.736(\delta) - 14.7 \left(1 - \frac{1}{\delta} \right)^{3.74} + 4.8(\delta)^{-17.5} \quad (\text{A-2})$$

For the case of $\delta=1.06$, f_w was assumed equal to its minimum limit ($\delta=1.125$).

The surface of particles to reactor volume ratio, α , was estimated as in Equation A-3 [291].

$$\alpha = 4 \frac{A_{s,\text{total}}}{l_{\text{reactor}} D^2 \pi} \quad (\text{A-3})$$

Table A-1 reports the values of the aforementioned parameters, along with the hydraulic diameter, d_h (Equation 3-9) for all configurations.

Table A-1. Values of model parameters.

δ (-)	ε (-)	f_w (-)	α (-)	d_h (mm)
1.06	0.401	1.435	3911.6	0.384
1.20	0.530	1.063	3062.9	0.428
1.40	0.630	0.908	2388.3	0.443
1.68	0.678	0.739	2047.9	0.496

A3. Choice of number of crescent sections for microscopic approach

Each sphere in a SPSR can be dissected into an infinite number of crescent sections, each representing the mass transfer coefficient at a specific point. The greater the number of crescent sections, the more precise the analysis would be. However, as a compromise between time efficiency, the level of detail required for accuracy and the computational resources available, cases with 16 and 32 crescent sections were analysed. In Figure A-5, the local concentration at 3 μm away from the particle surface vs the studied angles of the

corresponding crescent sections is presented for an SPSR with $\delta=1.06$ and $Re_h=5$. As observed in Figure A-5, the choice of 16 crescent sections adequately captured the main trends and was therefore selected for the microscopic analysis.

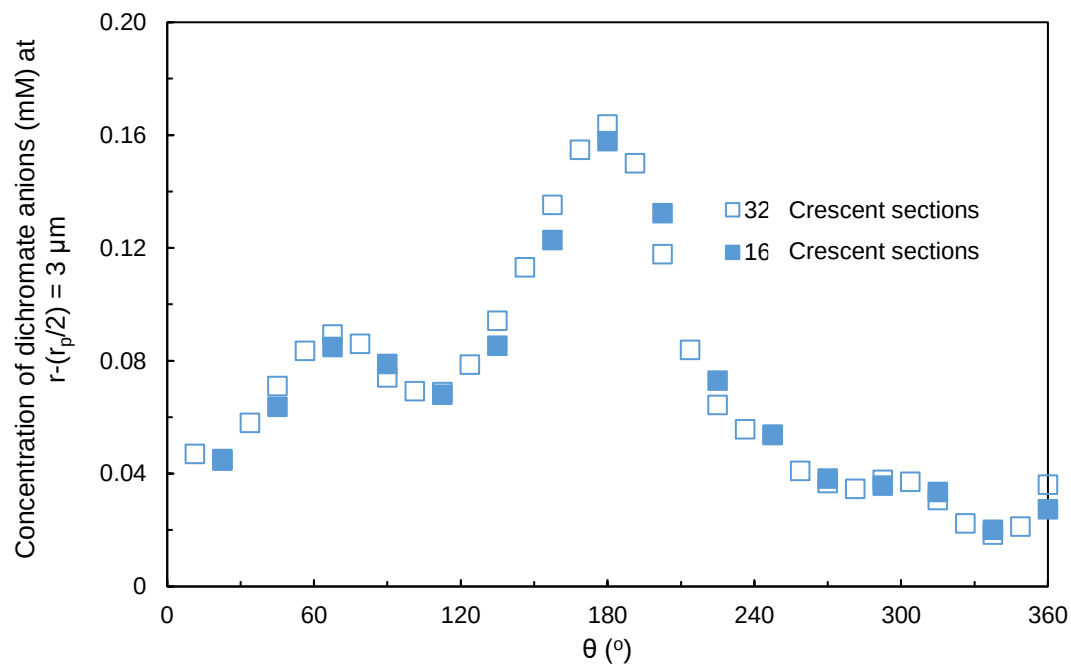


Figure A-5. Dichromate anion concentration variation across crescent sections for different numbers of sections in the liquid-to-solid mass transfer microscopic approach.

Appendix B: Esterification of levulinic acid to ethyl levulinate over Amberlyst-15 in flow: Systematic kinetic model discrimination and parameter estimation (SI from Chapter 4)

B1. NMR spectroscopy analysis

Nuclear Magnetic Resonance (NMR) spectroscopy was used to guarantee that no side-reactions were taking place under the experimental conditions investigated. For this reason, a sample was collected in the waste vessel, after the experiment ran for more than an hour to ensure that steady state conditions were achieved. A mixture of a similar composition was created using reactants and products purchased from the suppliers. Analysis was conducted with D₂O as the solvent. The spectra of ¹H NMR analysis are shown in

Figure B-1 B-1, whereas the spectra of the ¹³C NMR are presented in Figure B-2. Although the intensity of the peaks is different due to the slightly different concentrations of the mixtures, it is important to note that the study focused on the qualitative analysis of the samples. Therefore, the only difference between the reaction mixture and the prepared solution can be observed for the ¹H NMR analysis at a shift of +2.04 ppm, a peak that also appears in the ¹³C NMR spectrum at +1.36 ppm and +119.46 ppm.

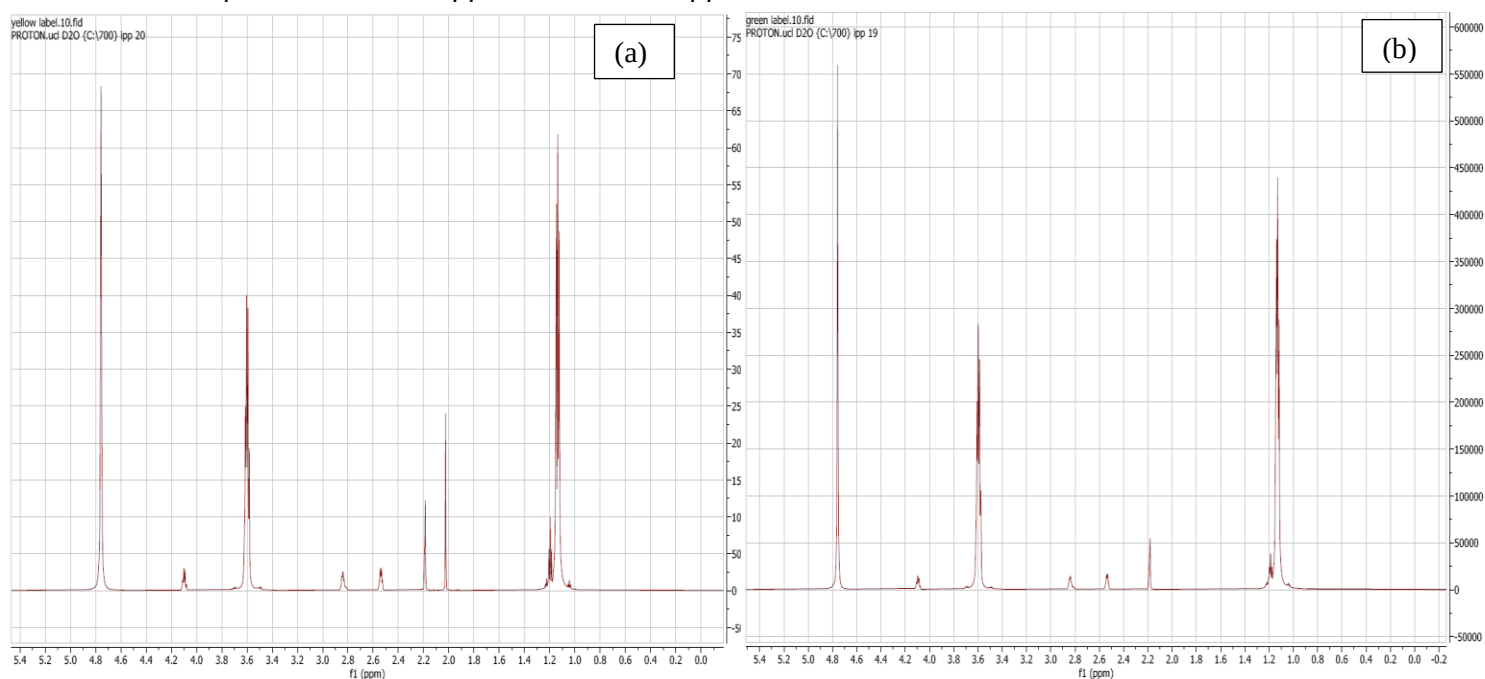


Figure B-1. ¹H NMR spectra of (a) the effluent of the reactor and (b) pre-made solution of similar concentration.

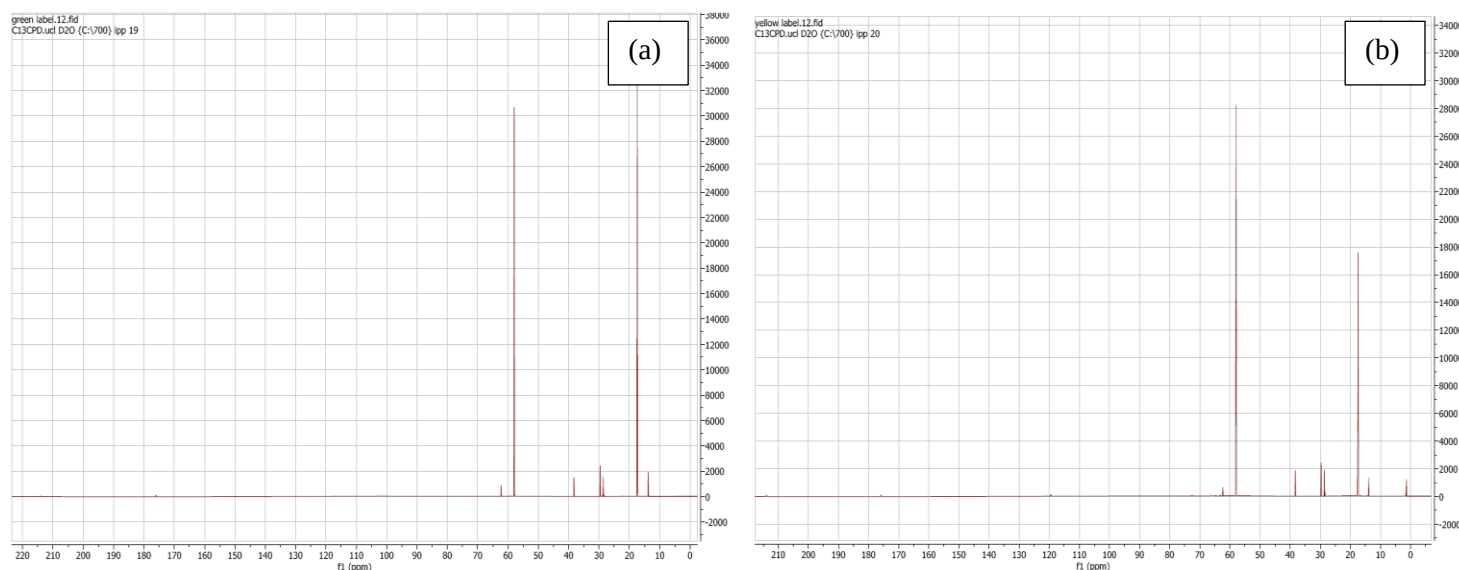


Figure B-2. ^{13}C NMR spectra of (a) the effluent of the reactor and (b) pre-made solution of similar concentration.

Based on the NMR chemical shifts of impurities [476], the shift of the peaks can be attributed to the proton of CH_3 (for ^1H NMR) and the carbon of CN and CH_3 (for ^{13}C NMR) of acetonitrile. Acetonitrile cannot be formed as a by-product of the reaction, based on the possible reaction pathways [477-479]. Given that a mixture of acetonitrile and water were used as mobile phase for the HPLC analysis, traces of it potentially entered the system (after the exit of the reactor) in the sample loop of the HPLC sampler and autodilutor and got collected in the waste vessel.

B2. Experimental results

The experimental results obtained from the fractional factorial experimental design are presented in Table B-1 to Table B-4 for both experimental sets 1 and 2.

Table B-1. LA measured concentration at the reactor outlet from three campaigns, each campaign consisting of eight experiments. Data produced without addition of water in the feed solution (Experimental Set 1).

Experiment	Temperature (° C)	Flowrate ($\mu\text{l}/\text{min}$)	Inlet concentration (M)	Outlet LA concentration (M) Campaign			Average outlet LA concentration (M)
				1	2	3	
1	70	20	0.8	0.377	0.401	0.389	0.389
2	70	20	1.6	0.870	0.910	0.894	0.891
3	70	60	0.8	0.631	0.624	0.610	0.622
4	70	60	1.6	1.315	1.305	1.302	1.307
5	100	20	0.8	0.059	0.066	0.073	0.066
6	100	20	1.6	0.192	0.208	0.229	0.210
7	100	60	0.8	0.301	0.305	0.311	0.306
8	100	60	1.6	0.695	0.710	0.701	0.702

Table B-2. EL measured concentration at the reactor outlet from three campaigns, each campaign consisting of eight experiments, as given in Table B-1. Data produced without addition of water in the feed solution (Experimental Set 1).

Experiment	Outlet EL concentration (M) Campaign			Average outlet EL concentration (M)
	1	2	3	
1	0.425	0.418	0.415	0.419
2	0.741	0.695	0.704	0.714
3	0.193	0.187	0.187	0.189
4	0.332	0.312	0.319	0.321
5	0.746	0.743	0.728	0.739
6	1.390	1.407	1.350	1.382
7	0.499	0.492	0.475	0.489
8	0.895	0.876	0.883	0.885

Table B-3. LA measured concentration at the reactor outlet from three campaigns, each campaign consisted of eight experiments. Data produced with the addition of water in the feed solution (Experimental Set 2).

Experiment	Temperature (° C)	Flowrate (μ l/min)	Inlet concentration (M) LA	Inlet concentration (M) H ₂ O	Outlet LA concentration (M) Campaign			Average outlet LA concentration (M)
					1	2	3	
1	70	20	0.8	4.18	0.637	0.658	0.632	0.642
2	70	20	1.6	4.23	1.274	1.312	1.261	1.293
3	70	60	0.8	4.18	0.745	0.763	0.760	0.756
4	70	60	1.6	4.23	1.522	1.517	1.553	1.531
5	100	20	0.8	4.18	0.245	0.288	0.261	0.266
6	100	20	1.6	4.23	0.595	0.614	0.615	0.608
7	100	60	0.8	4.18	0.518	0.557	0.532	0.537
8	100	60	1.6	4.23	1.090	1.093	1.125	1.103

Table B-4. EL measured concentration at the reactor outlet from three campaigns, each campaign consisted of eight experiments, as given in Table B-3. Data produced with the addition of water in the feed solution (Experimental Set 2).

Experiment	Outlet EL concentration (M) Campaign			Average outlet EL concentration (M)
	1	2	3	
1	0.165	0.153	0.144	0.154
2	0.284	0.293	0.265	0.281
3	0.055	0.048	0.063	0.055
4	0.109	0.101	0.107	0.106
5	0.490	0.519	0.501	0.505
6	0.930	0.917	0.919	0.922
7	0.266	0.252	0.258	0.259
8	0.479	0.508	0.466	0.485

B3. Solubility limits of levulinic acid in ethanol and water

To guarantee that with the introduction of water in the inlet feed, there was no formation of a two-phase solution inside the syringes, the solubility limits of LA in ethanol and water were calculated separately based on the work of Jakob et al. [480] and Apeblat and Manzurola [481], respectively. In this way, the maximum concentration of LA in the inlet feed was set, since ethanol is miscible in liquid water at all concentrations at room temperature and atmospheric pressure [482]. At 25°C, the solubility of LA in EtOH is equal to 930 g L⁻¹ and the mole fraction solubility of LA in H₂O (defined as the ratio of the number of moles of LA over the sum of the number of moles of the LA and H₂O) is 0.4484.

Based on the molecular weight and density of LA, EtOH and H₂O presented in Table B-5, the maximum concentration of LA in ethanol was equal to 4.40 M and LA in H₂O was 8 M respectively. Therefore, inlet concentrations of 0.8 M and 1.6 M, loaded in the stainless-steel syringes, were considered within the limits of solubility.

Table B-5. Properties of LA, EtOH and H₂O for the calculation of maximum solubility of LA in each solvent.

	MW (g/mol)	Density (g/mL)
LA	116.12	1.134
EtOH	46.07	0.789
H ₂ O	18.02	1.000

B4. Preliminary equilibrium calculations

Prior to the introduction of water in the feed solution for Experimental Set 2, a preliminary estimation of whether the reaction could be considered reversible given the inlet

concentrations of the components was conducted. Based on the kinetics reported by Russo et al. [345] for the same reaction in batch, considering a pseudo-homogeneous first order reaction, the equilibrium constant was expressed by Equation B-1.

$$K_{eq} = 3.18e^{\frac{-15.14 \cdot 10^3}{8.314} \left(\frac{1}{T} - \frac{1}{333} \right)} \quad (B-1)$$

where, T is the temperature.

Therefore, for the worst-case scenario, which is the one of higher temperatures (100 °C in this work), the equilibrium constant K_{eq} can be calculated equal to 5.71.

The equilibrium constant K_{eq} can also be expressed as follows

$$K_{eq} = \frac{C_W \cdot C_{EL}}{C_{LA} \cdot C_{EtOH}}. \quad (B-2)$$

Substituting the values of experimental conditions 5-8 of Table B-3 and Table B-4 in Equation B-2, the values of the K_{eq} are reported in Table B-6. The higher K_{eq} was found for experimental condition 5 equal to 0.64.

Table B-6. Outlet concentrations of reactants (LA and EtOH) and products (EL and H₂O) and calculated value of the equilibrium constant, K_{eq} .

Experiment	Outlet concentration (M) LA	Outlet concentration (M) EL	Outlet concentration (M) H ₂ O	Outlet concentration (M) EtOH	K_{eq}
5	0.266	0.505	4.446	13.932	0.606
6	0.608	0.922	4.838	12.097	0.606
7	0.537	0.259	4.717	14.178	0.160
8	1.103	0.485	5.333	12.534	0.187

Hence, it can be safely assumed that the conditions studied were far away from equilibrium.

B5. Model fitting statistics

The following tables contain the quantitative model fitting information in the form of the LoF metric, the chi-square value (χ^2) and its respective threshold value (χ^2_{ref}) from a χ^2 test with a 95% significance level and $N_{exp} \cdot N_y - N_\theta$ degrees of freedom (DoF). Data of Table B-7 is presented graphically in Figure 4-9 to Figure 4-11 of the main chapter and the data of Table B-8 is depicted in Figure 4-12(a-c).

Table B-7. Model fitting statistics based on the LoF calculation (χ^2 test) by means of χ^2 and χ^2_{ref} values for the different experimental spaces explored in this work: Experimental Set 1 (without water in the feed), Experimental Set 2 (with water in the feed) and combination of Experimental Sets 1 and 2.

Model No.	Experimental Set 1		Experimental Set 2		Experimental Set 1 and 2 combined	
	χ^2	χ^2_{ref}	χ^2	χ^2_{ref}	χ^2	χ^2_{ref}
Model 1	192.8	62.8	176.7	60.5	6640.2	115.4
Model 2	3190.9	62.8	991.6	60.5	10636.6	115.4
Model 3	56.2	58.1	80.3	55.8	187.7	110.9
Model 4	56.2	59.3	102.7	56.9	220.9	112.0
Model 5	56.2	59.3	80.3	56.9	6408.8	112.0
Model 6	192.8	60.5	176.7	58.1	6640.2	113.1
Model 7	56.2	59.3	100.3	56.9	193.3	112.0
Model 8	56.2	60.5	109.4	58.1	220.9	113.1
Model 9	56.2	60.5	100.3	58.1	6408.8	113.1
Model 10	192.8	61.7	176.7	59.3	6640.2	114.3
Model 11	56.7	59.3	80.3	56.9	187.7	112.0
Model 12	56.7	60.5	102.9	58.1	220.9	113.1
Model 13	56.7	60.5	80.3	58.1	6411.2	113.1
Model 14	192.8	61.7	176.7	59.3	6640.2	114.3
Model 15	56.7	60.5	100.3	58.1	193.3	113.1
Model 16	56.7	61.7	109.4	59.3	220.9	114.3
Model 17	56.7	61.7	100.3	59.3	6411.2	114.3
Model 18	56.5	59.3	100.7	56.9	183.3	112.0
Model 19	56.5	60.5	124.3	58.1	201.1	113.1
Model 20	56.5	60.5	100.7	58.1	6409.0	113.1
Model 21	192.8	61.7	176.7	59.3	6640.2	114.3
Model 22	56.9	59.3	82.0	56.9	178.9	112.0
Model 23	56.9	60.5	124.3	58.1	201.1	113.1
Model 24	56.9	60.5	82.0	58.1	6411.3	113.1
Model 25	192.8	61.7	176.7	59.3	6640.2	114.3
Model 26	56.9	60.5	103.8	58.1	183.3	113.1
Model 27	56.9	61.7	124.4	59.3	201.1	114.3
Model 28	56.9	61.7	100.7	59.3	6411.3	114.3

Table B-8. Model fitting statistics based on the LoF calculation (χ^2 test) by means of χ^2 and χ_{ref}^2 values for the reformulated models with the minimum χ^2 of Table S8. The χ^2 and χ_{ref}^2 values are calculated for the combined experimental sets on the hypothesis of a) Constant adsorption equilibrium parameters, b) Temperature dependency of the adsorption equilibrium parameters for water and EL and c) Temperature dependency of the adsorption equilibrium constant only for water.

Model No.	Constant adsorption equilibrium for water and EL		Temperature dependency of adsorption equilibrium for water and EL		Temperature dependency of adsorption equilibrium for water and constant adsorption equilibrium for EL	
	χ^2	χ_{ref}^2	χ^2	χ_{ref}^2	χ^2	χ_{ref}^2
Model 15	193.3	113.1	127.1	110.9	127.4	112
Model 16	220.9	114.3	144.2	113.1	144.2	113.1
Model 26	183.3	113.1	135.5	110.9	136.8	112
Model 27	201.1	114.3	142.5	113.1	142.5	113.1

B6. Automated platform development via LabVIEW

The LabVIEW code developed in this study facilitated the execution of a range of experimental conditions, including conducting a series of steady-state experiments (Figure B-3). The LabVIEW code executed each experimental condition for a user-defined duration to ensure the reactor achieved steady-state. Upon reaching the specified time limit, the code retrieved the most recent HPLC measurement, considering it as the steady-state outlet concentration for that condition. Subsequently, both the experimental conditions and outlet concentrations were logged in an Excel file along with previous experimental data. Additionally, the LabVIEW code continuously monitored and recorded temperatures, flowrates, and pressures, saving the data in a separate Excel file for subsequent analysis. Safety shutdown mechanisms were integrated into the LabVIEW code to automatically halt the operation of pumps and heaters if any temperature or pressure surpassed user-defined thresholds.

Fundamentally, the LabVIEW program consists of two core components: the "block diagram," housing the logic, and the "front panel," serving as the user interface. Figure B-3 illustrates the front panel interface used in this LabVIEW code. The actual values of the conditions were displayed, as well as the concentrations for levulinic acid (LA) and ethyl levulinate (EL) at the end of each run, based on the area of the respective chromatogram and their calibration curves (Appendix B9). Temperature and pressure were monitored both by displaying their real-time values and their evolution with time in graphs.

The graphical programming language of LabVIEW employs logical and loop structures, replacing traditional lines of code. In this project, four key loop elements were utilised: a "timed loop", a "flat sequence structure", a "case structure", and a "while loop".

The “timed loop” efficiently repeats a set of commands at a specified frequency until the experimental duration limit is reached or the safety limits are exceeded, thereby controlling the execution cycle and facilitating the monitoring and comparison of set values to process values within the stipulated period for each experiment. The experimentalist can choose the frequency of the “timed loop”, which in this work was set to 5 s for execution that translated to 600 cycles for an experiment duration of 50 min.

The “flat sequence structure” facilitates the sequential execution of events, with frames executed in a well-defined order. For each experiment, the Python code accesses previously stored HPLC result, initiating the sequence. Subsequently, it proceeds to update the record file with details of the experimental conditions and outlet composition, recorded in an Excel file. The final command in the “flat sequence” relays the next pre-planned experimental condition to the hardware through the “timed loop”.

Within the “case structure”, multiple sub-diagrams contain sets of commands executed for each experiment. Considering there were nine pre-planned experiments (eight distinct experimental conditions plus the repetition of the first one), nine sub-diagrams were found within the “case structure”. An extra tenth “case structure” was added as the default setting.

The above-mentioned loops and structures operate within a while loop, overseeing repetitive operations in a virtual instrument (VI) until all planned experiments are executed. Upon completion, the platform reverts to default settings, marked by a temperature of 20°C and zero flowrate for reactants in this work. The automated process concludes when the while loop terminated, triggered either by activating the stop button in the LabVIEW front panel or when the iteration number in the while loop equalled the number specified for the default setting in the case structure.

For better comprehension of the LabVIEW code, the algorithm is provided in Figure B-4. The integration of LabVIEW and Python enabled efficient execution, monitoring, and analysis of steady-state experiments, providing a robust platform for experimental design and data acquisition.

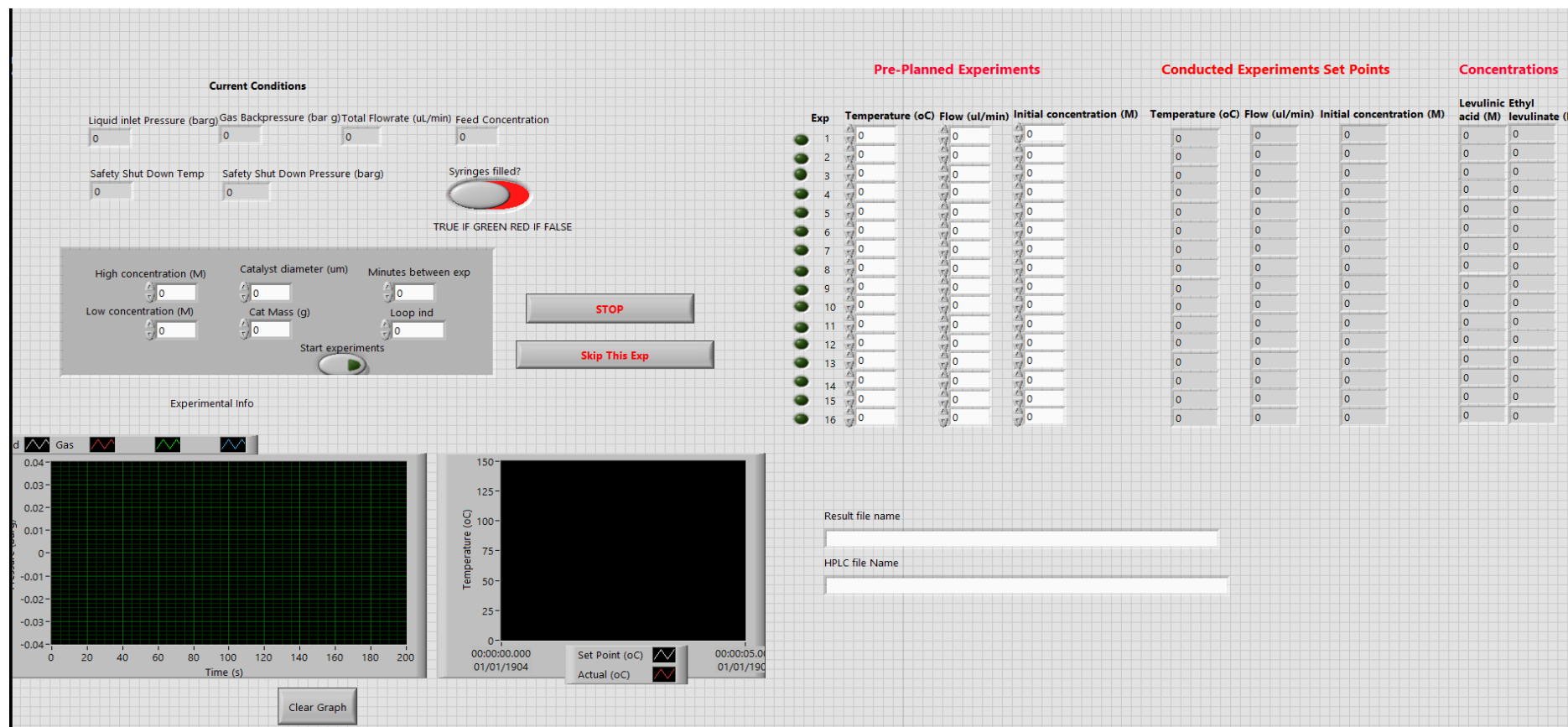


Figure B-3. LabVIEW user interface. The running experimental conditions are displayed, as well as the set of the pre-planned experiments and the concentration of EL and LA at the outlet of the reactor at the end of each run. Temperature and pressure are monitored through real-time running graphs.

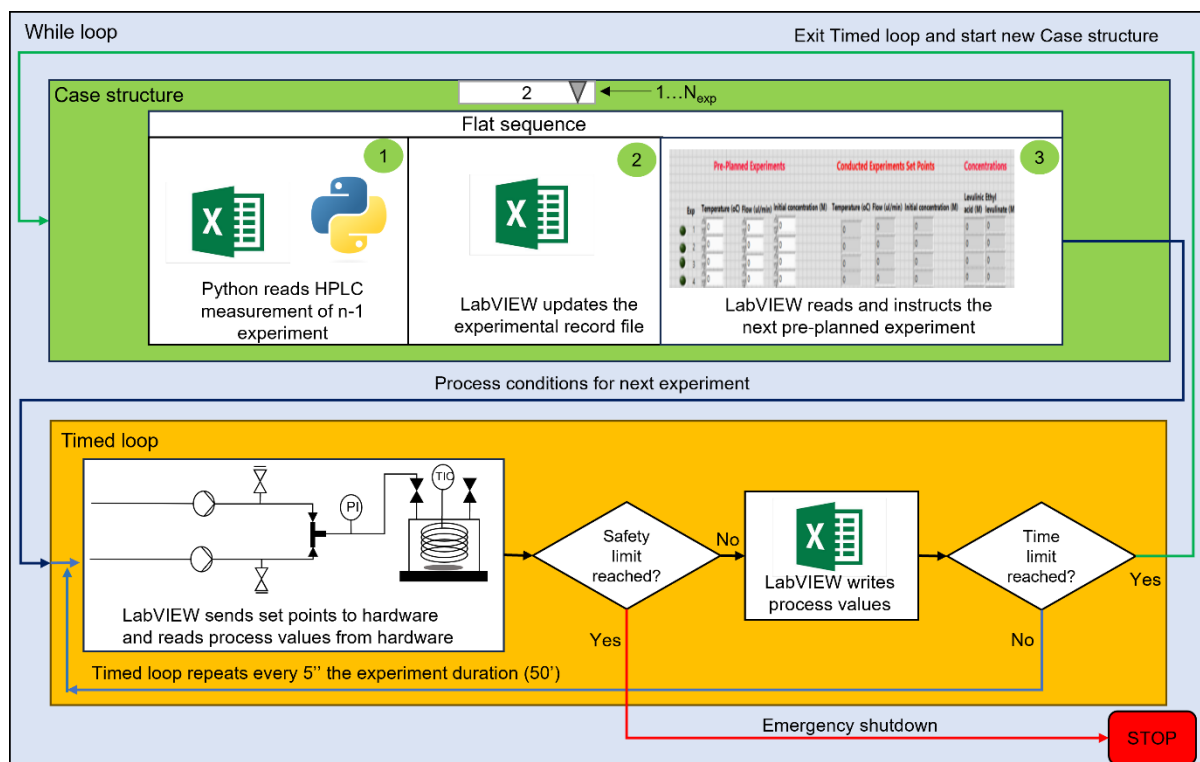


Figure B-4. Simplified LabVIEW block diagram implemented for automation, showing the flow of information and the four loop elements: While loop, Case structure, Timed loop and Flat sequence.

B7. HPLC calibration curves for LA and EL

As HPLC equipped with a UV-Vis detector is crucial for both qualitative and quantitative analysis, determining the optimal wavelength for levulinic acid (LA) and its ester (EL) is essential. Initially, absorbance measurements of levulinic acid and ethyl levulinate were conducted using a UV-Vis spectrometer (Ocean Optics UV-vis-ES USB 2000+ spectrometer with an Ocean Optics DH-2000BAL light source) in quartz cuvettes. LA exhibited maximum absorption at 266 nm in water, while its interaction with ethanol shifted the wavelength to 271 nm. Similarly, EL showed optimal absorption at 270 nm in water and 275 nm in ethanol. Consequently, wavelengths of 271 nm and 275 nm were deemed suitable for HPLC channels.

These findings were corroborated with HPLC (Jasco LC-4000) UV-Vis detector results, where absorbance measurements were made without the HPLC column to expedite the process. It was determined that the optimal wavelengths for LA and EL were 272 nm and 274 nm, respectively. Although these wavelengths are close, the measured areas showed no significant difference, as depicted in Figure B-5. Thus, a calibration curve for levulinic acid and ethyl levulinate absorbance was established at 272 nm..

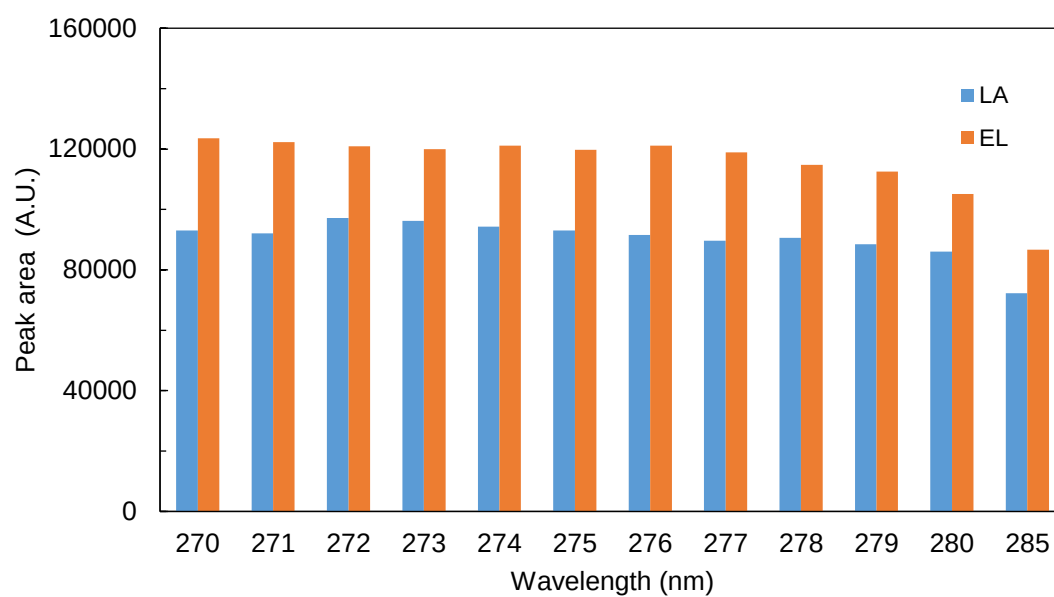


Figure B-5. Peak area vs detector wavelength for LA and EL, measured by the HPLC (Jasco LC-4000) UV-vis detector.

Appendix C: Inline Reaction Kinetics in a Miniaturised CSTR using Raman Spectroscopy (SI from Chapter 5)

C1. Details of reactor components and fabrication of Raman holder

- Reactor components³

The reactor components were designed and machined to ensure precise functionality and seamless integration. The following details describe the specifications of each component:

a) Cooling/heating jacket

- Material: 316 Stainless Steel.
- Dimensions: Finished dimensions are 90 mm x 90 mm x 24.65 mm (w x l x h).
- Features:
 1. Machined pocket: A pocket with a 68 mm diameter and a protruding section to aid liquid flow.
 2. O-Ring seal: Fitted with an FKM O-ring (76 mm OD x 72 mm ID x 2 mm thick) to seal between the reactor and the inner reactor.
 3. Mounting holes: Four M4 holes drilled and tapped 15 mm deep, equally spaced around the inner pocket.
 4. Inlet and outlet holes: Two threaded holes for liquid inlet and outlet, compatible with $\frac{1}{4}$ R (taper) hexagon hose nipple fittings with an 8 mm barbed hose connection.

b) Reactor chamber with inlet and outlet ports

- Material: 316 Stainless Steel.
- Dimensions: Finished dimensions are 79.90 mm x 79.90 mm x 33 mm (w x l x h).
- Features:
 1. Boss: A 44 mm diameter boss for clearance fit between the inner reactor and reactor base.
 2. Top pocket: A rectangular pocket (6 mm deep) to house the reactor lid and create a seal between the glass and reactor lid from the bottom.
 3. Optical window pocket: A circular machined pocket to house the optical window, with a recessed circular frame for an FKM O-ring (23 mm OD x 20 mm ID x 1.5 mm).

³ The fabrication of the reactor components and the development of the CAD designs were made possible with the support of Mr. Simon Dawes from the Workshop of Biochemical, Chemical Engineering, and Physics at University College London.

4. Main chamber: The main chamber has a 15 mm diameter and 15 mm depth, with three holes (two drilled at an angle to the bottom and one near the top).
5. Upstands: Three upstands on the top, drilled and threaded to suit ¼"-28 UNF Peek fittings.

c) Reactor cover

- Material: 316 Stainless Steel
- Dimensions: Finished dimensions are 30 mm x 27.5 mm x 12.50 mm (w x l x h).
- Features: Multiple machined areas and 3 mm through holes for fitting over the jacket's machined pocket section to minimise heat losses.

- Raman holder

A simple and sturdy holder for housing the Raman probe was designed⁴ and fabricated to enable reliable data acquisition by minimising external vibrations that can interfere with the Raman laser. The holder base, as presented in Figure C-1, is cylindrical with a circular cross-section of 5.1 cm in diameter (shell of 1 cm thickness) to accommodate the Raman probe. Additionally, it features a circular aperture of 1.5 cm on the bottom for the tip of the probe, and four small blind holes symmetrically added to the base for the installation of support legs. This design approach can be customized to suit the specific requirements of the application.

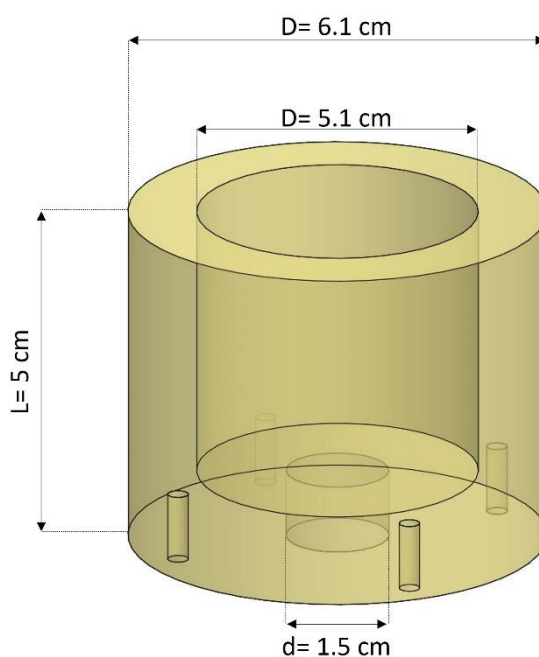


Figure C-1. Dimensions of the in-house custom-made Raman probe holder.

⁴ The Raman holder was designed by Ms. Maria Mourkou at the Department of Chemical Engineering, UCL.

The 3D printer used is a FormLabs Form 3 3D printer. The SLA 3D printer has a laser power of 250 mW and a laser spot size of 85 μm (with 25 μm XY resolution), while the selected layer thickness is 0.1 mm, which reduces the amount of printing time to approx. 6 hours. The material chosen for the 3D printing is a high-temperature resin. This photopolymerization resin has high thermal stability, which is suitable to withstand any heat originating from the laser, without any substantial deformation. The 3D printing procedure is followed by post-processing steps that include chemical cleaning by bathing in an isopropanol tank for 6 minutes according to FormLabs instructions [483] to remove uncured resin from the surface of the part, and post-curing. For high-temperature resin parts, post-curing is performed in a UV curing station provided by FormLabs at 80°C for 2 hours [484].

Metallic threads are added as support legs in the body of the holder to provide adequate mechanical stability during experimentation. It is worth noting that the threading of the blind holes located on the base of the Raman probe holder was drilled manually with a thread cutter after 3D printing and post-processing to ensure the perfect fitting of the metallic support legs. The initial 3D design and real-life assembly are shown in Figure C-2.

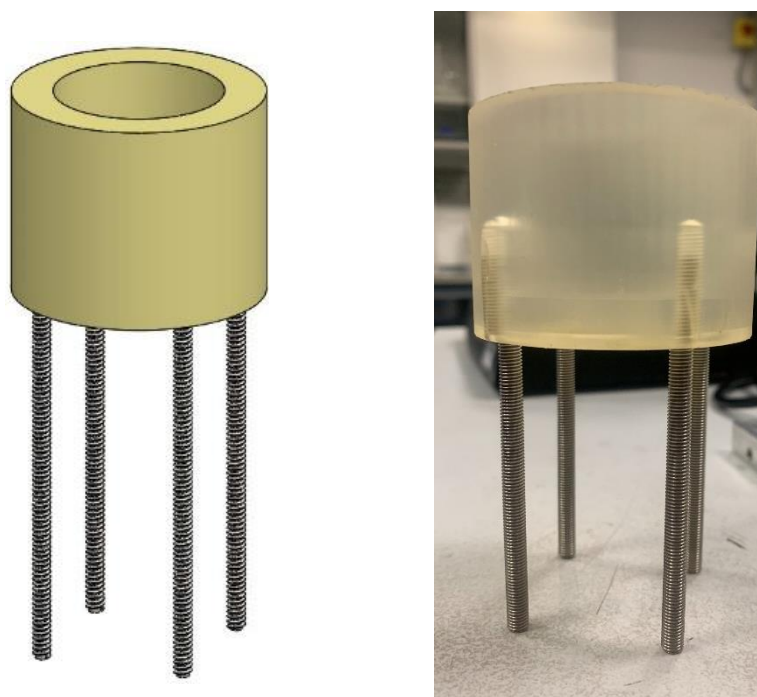


Figure C-2. 3D design concept of the Raman holder (left) and real-life execution (right).

C2. Integration of Huber circulator in LabVIEW⁵

Integrating the Huber circulator (CC-K6 with Pilot One) into LabVIEW presented a notable challenge due to several factors. Firstly, the Huber circulator lacked any provision for direct connection with external type-K thermocouples, which are typically used to monitor and control the setpoint temperature within the reactor chamber. Additionally, the PID controller embedded within the Huber system, responsible for finely adjusting the temperature of the bath, was inaccessible to users and could not be modified to address safety concerns such as temperature overshooting.

To overcome these limitations, an alternative strategy was devised. This involved the integration of an external type-K thermocouple with an Arduino device, which was subsequently interfaced with LabVIEW to establish control over the Huber circulator's setpoint. Specifically, an Adafruit thermocouple amplifier (Max31855) was soldered onto a stripboard alongside an Arduino Nano, with communication established via the SPI protocol. The Arduino was programmed to output serial data containing the internal temperature readings from the Adafruit amplifier, as well as the temperature readings from the attached type-K thermocouple.

In the LabVIEW environment, this serial data stream was captured and processed, enabling real-time monitoring and control of the temperature parameters. By developing a LabVIEW PID controller, the setpoint of the Huber circulator could be dynamically adjusted based on the feedback received from the external thermocouple. This indirect control mechanism allowed for precise regulation of the temperature within the reactor chamber, circumventing the limitations imposed by the inaccessible PID controller within the Huber system. Selecting parameters using the Ziegler-Nichols method [485], along with intuition and experimentation, led to the determination of optimal values for the PID controller. Through this process, the proportional gain (K_p) was set to 1, the integral gain (K_i) was also set to 1, and the derivative gain (K_d) was determined to be 0.0625.

C3. Estimation of measurement error

It is assumed that the measured responses of a true model adequately describing the reaction rate are corrupted with uncorrelated normally distributed measurement error with zero mean and certain standard deviation, Σ , which is attributed solely on the system response variables and not on systematic bias or error from other sources like imperfect input control.

⁵ The integration of Huber circulator in LabVIEW was accomplished with the assistance of Mr. Nicholas Snead from the Department of Chemical Engineering at UCL.

The standard deviation of the measurement error of each of the response variables s_{p_j} is calculated by the method of pooled standard deviation as the square root of the pooled variance.

$$\Sigma_{j,j} = s_{p_j}^2 = \frac{\sum_{i=1}^N s_{i,j}^2}{N} \quad \forall j = 1, \dots, N_y \quad (\text{C-1})$$

In Equation C-1, $s_{p_j}^2$ is the variance of the j -th response variable and $s_{i,j}^2$ is the variance of the j -th response variable in the i -th experimental condition calculated by Equation C-2.

$$s_{i,j}^2 = \frac{1}{n_i - 1} \sum_{k=1}^{n_i} (y_{k,j} - \bar{y}_{i,j})^2 \quad (\text{C-2})$$

Where, $\bar{y}_{i,j}$ is the mean of the j -th response variable in the i -th experimental condition with n_i data points.

C4. Post-processing of Raman spectra

The adaptive Iteratively Reweighted Penalized Least Squares (airPLS) algorithm, initially proposed by Zhang et al. [449], was employed for baseline correction due to its notable advantages of requiring no user intervention or prior knowledge of the system. The algorithm iteratively adjusts the weights of sum squared errors (SSE) between the fitted baseline and the original signals. The airPLS baseline estimator exhibits exceptional speed and flexibility in fitting baselines effectively. The tuning of the λ parameter, which controls the smoothness of the fitted baseline, was carried out through an intuitive approach. An important criterion for selecting the optimal λ value was ensuring that the fitted baseline did not include the peak regions of interest. The optimal λ value, determined to be 1000, was found to yield excellent baseline fits for the produced spectra.

The data processing was implemented using a custom MATLAB algorithm, which included the following steps:

1. Reading the data from the .txt files generated by the Marqmetrix Raman spectrometer.
2. Compiling the last five measurements for each experimental condition into an Excel file.
3. Applying the airPLS algorithm [449] for baseline correction in the spectral range of 600 to 2000 cm^{-1} , where the quartz glass window exhibited no discernible peaks.

4. Calculating the areas of benzaldehyde and the imine by integrating the spectral regions between 1679 to 1735 cm^{-1} and 1625 to 1675 cm^{-1} , respectively, for each of the five consecutive measurements in every experiment.
5. Implementing the Standard Normal Variate methodology [486] for baseline correction if fluctuations in intensity were observed during measurements, e.g. signal intensity decreasing in the case of prolonged low-temperature operation due to condensation of external humidity on the quartz window.

The effectiveness of the baseline correction procedure can be visualized in Figure C-3, which depicts a Raman spectrum before and after correction.

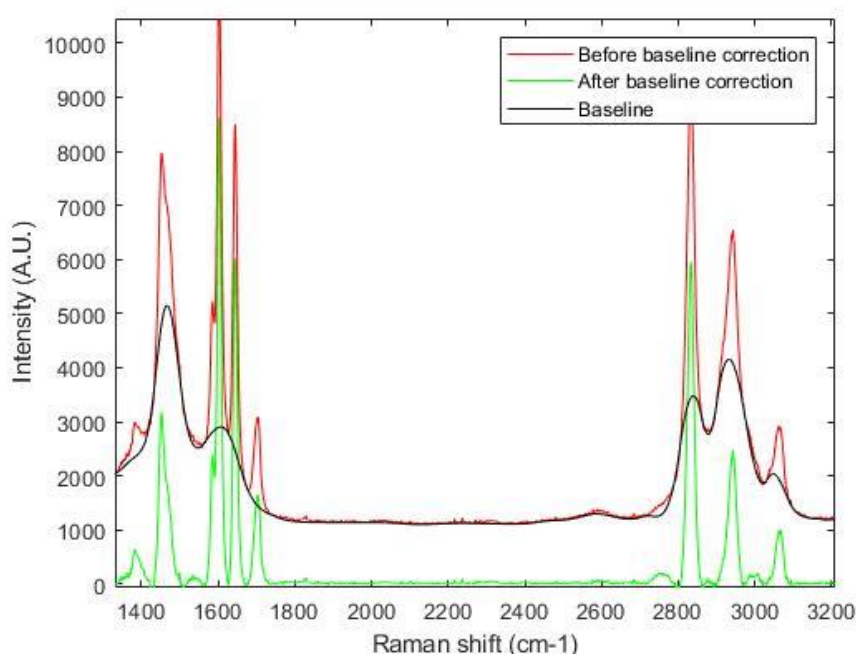


Figure C-3. Raman spectrum after baseline correction with the airPLS algorithm [449] in MATLAB. The red spectrum is the original data, the black line indicates the fitted baseline and the green spectrum is the baseline-corrected, final spectrum.

Furthermore, the successful implementation of this methodology is demonstrated in Figure C-4, showcasing the creation of calibration curves for the monitored components. These curves were constructed by preparing mixtures of these components in methanol to mimic the reaction conditions.

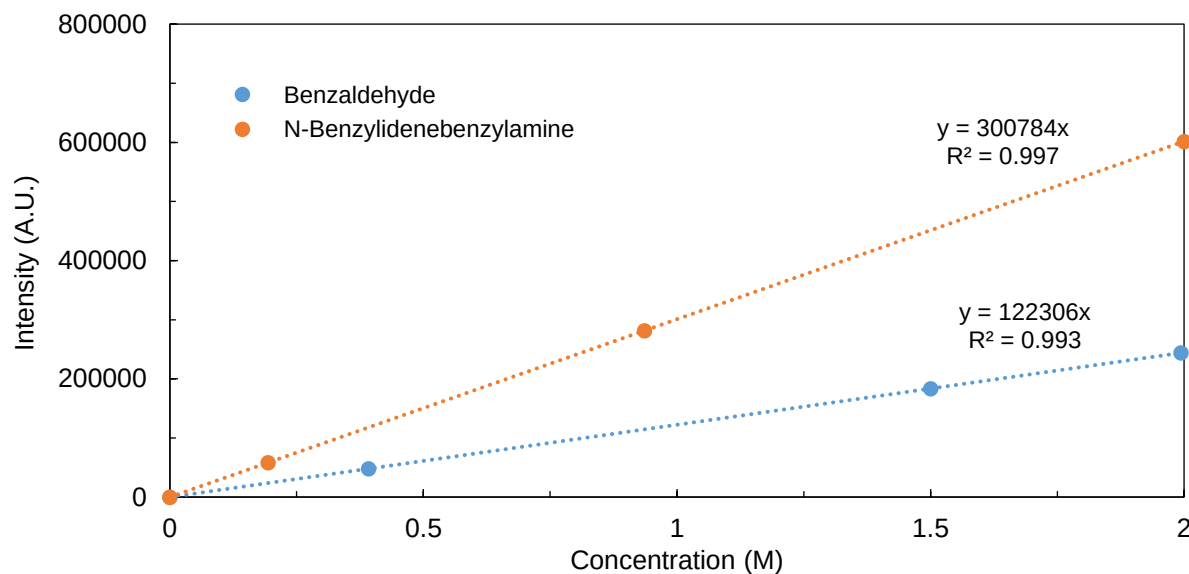


Figure C-4. Calibration curves for benzaldehyde (reactant) and *N*-benzylidenebenzylamine (product) in methanol for the range of concentrations used in the synthesis.

C5. Experimental measurements for the steady-state synthesis of *n*-benzylidenebenzylamine

The experimental results obtained from the factorial experimental design are presented in Table C-1 and Table C-2 for the reactant (benzaldehyde) and the product (*n*-benzylidenebenzylamine), respectively.

Table C-1. Benzaldehyde measured concentration at the reactor outlet from three campaigns, each campaign consisting of twelve experiments.

Experiment	Temperature (°C)	Flowrate (mL/min)	Inlet concentration of benzaldehyde (M)	Outlet concentration of benzaldehyde (M) Campaign			Average outlet concentration of benzaldehyde (M)
				1	2	3	
1	15	0.5	0.5	0.257	0.247	0.229	0.244
2	15	0.5	1	0.416	0.403	0.376	0.399
3	15	2	0.5	0.370	0.354	0.338	0.354
4	15	2	1	0.666	0.613	0.580	0.620
5	30	0.5	0.5	0.214	0.214	0.220	0.216
6	30	0.5	1	0.345	0.353	0.340	0.346
7	30	2	0.5	0.320	0.330	0.321	0.323
8	30	2	1	0.567	0.566	0.564	0.566
9	45	0.5	0.5	0.161	0.169	0.164	0.164
10	45	0.5	1	0.285	0.266	0.287	0.279
11	45	2	0.5	0.274	0.275	0.290	0.280
12	45	2	1	0.459	0.450	0.479	0.463

Table C-2. *N*-benzylidenebenzylamine measured concentration at the reactor outlet from three campaigns, each campaign consisting of twelve experiments.

Experiment	Temperature (°C)	Flowrate (mL/min)	Inlet concentration of benzaldehyde (M)	Outlet concentration of <i>n</i> -benzylidenebenzylamine (M) Campaign			Average outlet concentration of <i>n</i> -benzylidenebenzylamine (M)
				1	2	3	
1	15	0.5	0.5	0.269	0.286	0.280	0.278
2	15	0.5	1	0.642	0.654	0.663	0.653
3	15	2	0.5	0.152	0.148	0.158	0.153
4	15	2	1	0.346	0.383	0.392	0.374
5	30	0.5	0.5	0.325	0.334	0.331	0.330
6	30	0.5	1	0.677	0.727	0.715	0.706
7	30	2	0.5	0.194	0.195	0.204	0.197
8	30	2	1	0.436	0.468	0.482	0.462
9	45	0.5	0.5	0.358	0.358	0.356	0.357
10	45	0.5	1	0.755	0.778	0.781	0.771
11	45	2	0.5	0.226	0.239	0.248	0.238
12	45	2	1	0.535	0.547	0.556	0.546

C6. Preliminary study on the feasibility of employing a m-CSTR for heterogeneous liquid-solid reactions

As m-CSTRs are recognised for their adeptness in handling solids without encountering clogging issues [76], the m-CSTR unit developed in this study underwent testing for acquiring kinetic data of heterogeneously catalysed liquid reactions, utilising the Raman spectrometer probe. This investigation primarily aimed to evaluate the feasibility of acquiring Raman signals that could lead to the identification and subsequent quantification of reactants/products within a stirred chamber, where catalyst particles are continuously in motion. Consequently, a single experimental condition was explored across two distinct reactor operations: stopped-flow, analogous to a batch reactor, and continuous flow. The catalyst selected for the esterification of levulinic acid (LA) to ethyl levulinate (EL), as introduced in Chapter 4, comprised the commercially available sulfonic resin Amberlyst-15 with particle sizes ranging between 500-600 μm . Signals were acquired with a laser power of 300 mW every 2 seconds and a nickel mesh (Tecan, UK) of 25 μm thickness and 25 μm diameter holes was placed at the outlet to retain the catalyst.

The initial step involved obtaining the raw Raman spectra of LA (98%, Sigma Aldrich) in ethanol ($\geq 99.8\%$, Sigma-Aldrich) and EL (99%, Sigma-Aldrich) in ethanol separately, and the solvent (ethanol) alone, as shown in Figure C-5. The Raman shift was limited between 600 and 3200 cm^{-1} , where the quartz window does not display any significant Raman peaks. From Figure C-5, it is evident that the Raman spectrum of LA showed a characteristic peak at approximately 800 cm^{-1} that was not found in either ethanol or ethyl acetate [487]. The remaining peaks exhibited overlap between the two reaction components (water that was also part of the products is not measurable through Raman spectroscopy). Additionally, the peak intensity at 800 cm^{-1} was notably low, posing challenges for accurate quantification in lower concentrations.

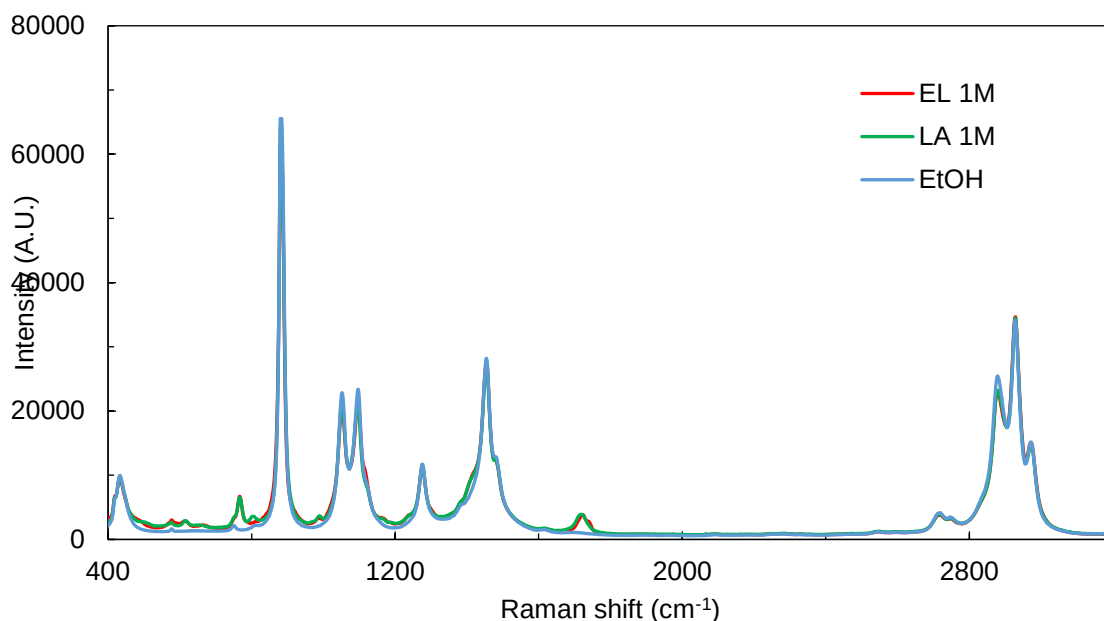


Figure C-5. Raman spectra for LA 1M in ethanol, EL 1M in ethanol and ethanol (solvent).

In Figure C-6, the Raman spectra of pure LA and EL are displayed. Notably, the differences in the Raman spectra of LA and EL were more pronounced when the two components were not diluted in ethanol. However, since these spectra were not representative of the actual reaction conditions, the esterification reaction chosen might have not been the best candidate reaction to perform and quantify the kinetics of with in-situ Raman spectroscopy. Nonetheless, it was still of interest to investigate how the signal changed when the catalyst particles were agitated within the reactor chamber in both continuous and stopped-flow operation. The experimental conditions studied are presented in Table C-3.

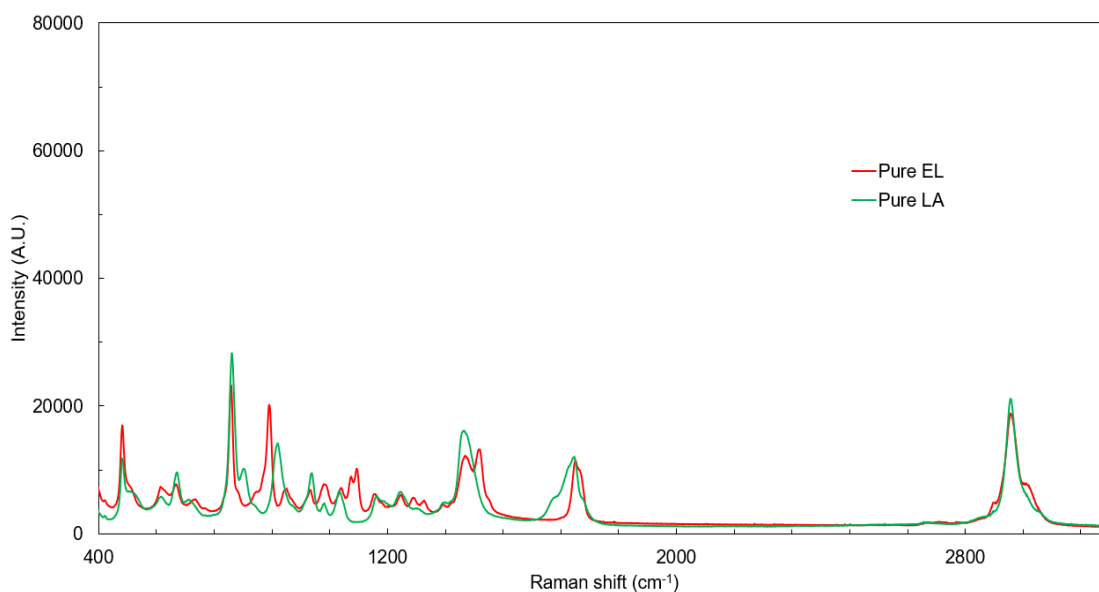


Figure C-6. Raman spectra for pure LA and pure EL.

Table C-3. Experimental conditions studied for the acquisition of Raman signal from a solution containing agitated solid catalyst particles.

Catalyst	Size (μm)	Catalyst mass (mg)	Mode	Flowrate ($\mu\text{L}/\text{min}$)	Temperature ($^{\circ}\text{C}$)	Initial LA concentration (M)
Amberlyst-15	500-600	25	Stopped-flow	-	70	1.6
Amberlyst-15	500-600	25	Continuous	100	70	1.6

In Figure C-7, both the raw Raman spectra and the baseline-corrected ones, obtained following the procedure described in Section C3, are depicted for continuous and stopped-flow operation of the m-CSTR. Although no significant change was observed in the calculated area of LA within the investigated 12-minute timeframe, Figure C-7 clearly demonstrates that the offset resulting from light scattering due to turbidity of the mixture and the presence of particles was effectively mitigated. This success enables the study of Raman-active heterogeneously catalysed reactions.

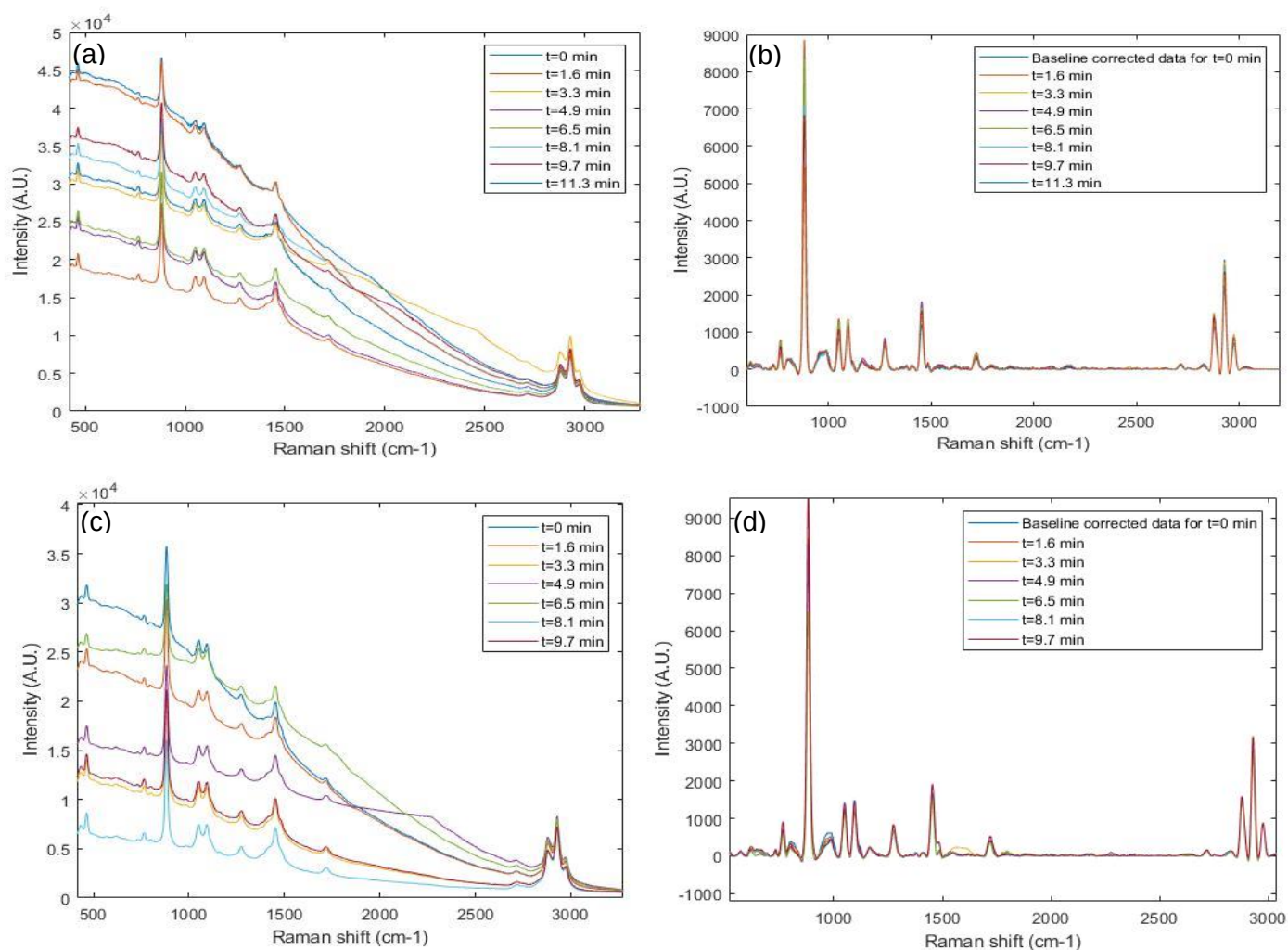


Figure C-7. Intensity of Raman peaks vs Raman shift at specific time intervals for continuous operation: (a) before baseline correction and (b) after baseline correction; and for stopped-flow operation: (c) before baseline correction and (d) after baseline correction, utilising the airPLS algorithm [449], for the esterification of LA to EL using Amberlyst-15 of the 500-600 μm sieve fraction.

The same reaction was also tested in continuous flow under the same conditions reported in Table C-1, using Strata X-C as a catalyst⁶, a strong cation exchange resin possessing the same functional sulfonic group ($-\text{SO}_3\text{H}$) linked to a benzene ring as Amberlyst-15 and Smopex-101 [345], both of which have been employed in the esterification reaction of LA to EL. The catalyst size was 100 μm , with 50 mg added to the reactor. A picture of the catalyst load inside the m-CSTR can be found in Figure C-8b. Due to the increased concentration of Strata X-C in comparison to Amberlyst-15, the intensity of the peaks decreased (Figure C-8a) and the peaks were not distinct. Given that the goal of acquiring a kinetic model involves quantifying the concentration of reactants and products, it is imperative to discern Raman photons from the solid matter against Raman signals originating from the pure liquid phase. Therefore, the optimum concentration and solid particles that can be used for kinetics coupled with Raman spectroscopy must be further investigated.

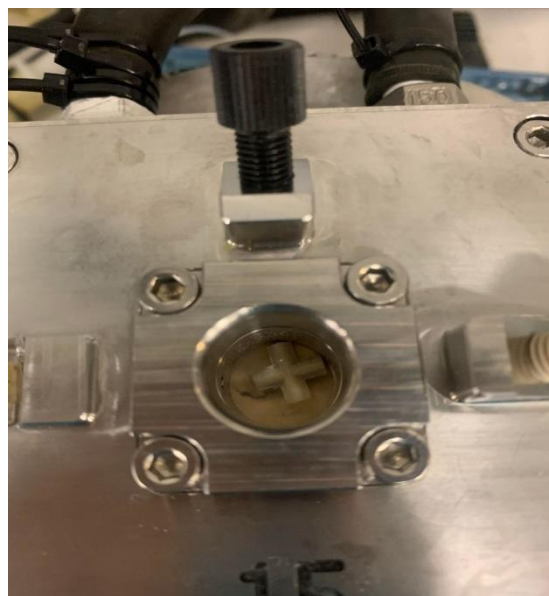
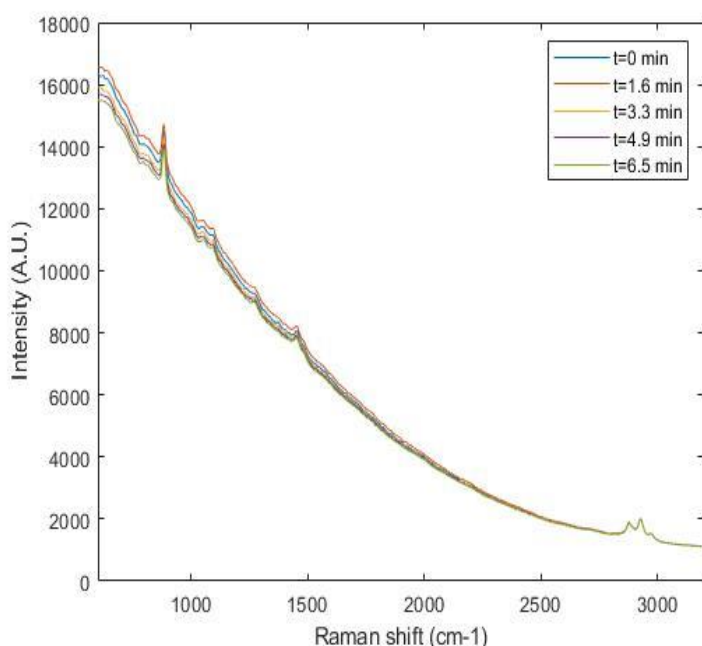


Figure C-8. (a) Raw data of the intensity of Raman peaks vs Raman shift at specific time intervals for continuous operation of the m-CSTR loaded with Strata XC of 100 μm diameter for the esterification of LA to EL. (b) Picture of the m-CSTR loaded with 50 mg of Strata X-C.

⁶ Strata X-C was kindly provided by Dr. Vincenzo Russo from the Chemical Sciences Department at the University of Naples Federico II.

C7. Comparison of Sliding Mesh with MRF approach

The Sliding Mesh model requires the partitioning of the computational domain into two distinct, non-overlapping sub-meshes; one rotating in sync with the impeller and the other remaining stationary, akin to the MRF method. While the sliding mesh approach provides superior accuracy in simulating rotating flows, it comes at the cost of substantial computational demands due to its reliance on transient calculations [445]. For this reason, as the aim of this work was to qualitatively simulate the flow field inside the m-CSTR, the SM approach was tested and compared against the MRF method for only one case ($Q = 0.25$ mL/min and $N = 250$ rpm). To further speed up the simulations, the flow field computed by the MRF model was used as an initial condition for the transient sliding mesh calculation. In Figure C-5, the velocity contours on a xz plane (plane perpendicular to one inlet and the outlet) of the transient simulation for different timestamps (and impeller angles, respectively), as well as that of the MRF approach, are portrayed. From Figure C-5, some important conclusions can be drawn. Firstly, it is apparent that the solution has reached steady-state as the velocity contours for each identical rotation (e.g. time = 1.68 s and time = 1.92s) were identical. Moreover, due to the geometry of impeller that had different number of tips for each consecutive side, in every impeller angle, the velocity field displayed a slight asymmetry. A comparison between the steady-state MRF approach and the transient experiments revealed that the velocity near the walls was higher when the frozen rotor model was used, which translated in an overestimation of the dissipation of turbulence. Given that the rest of the flow patterns were captured quite accurately, the MRF method was applied for the rest of the simulations.

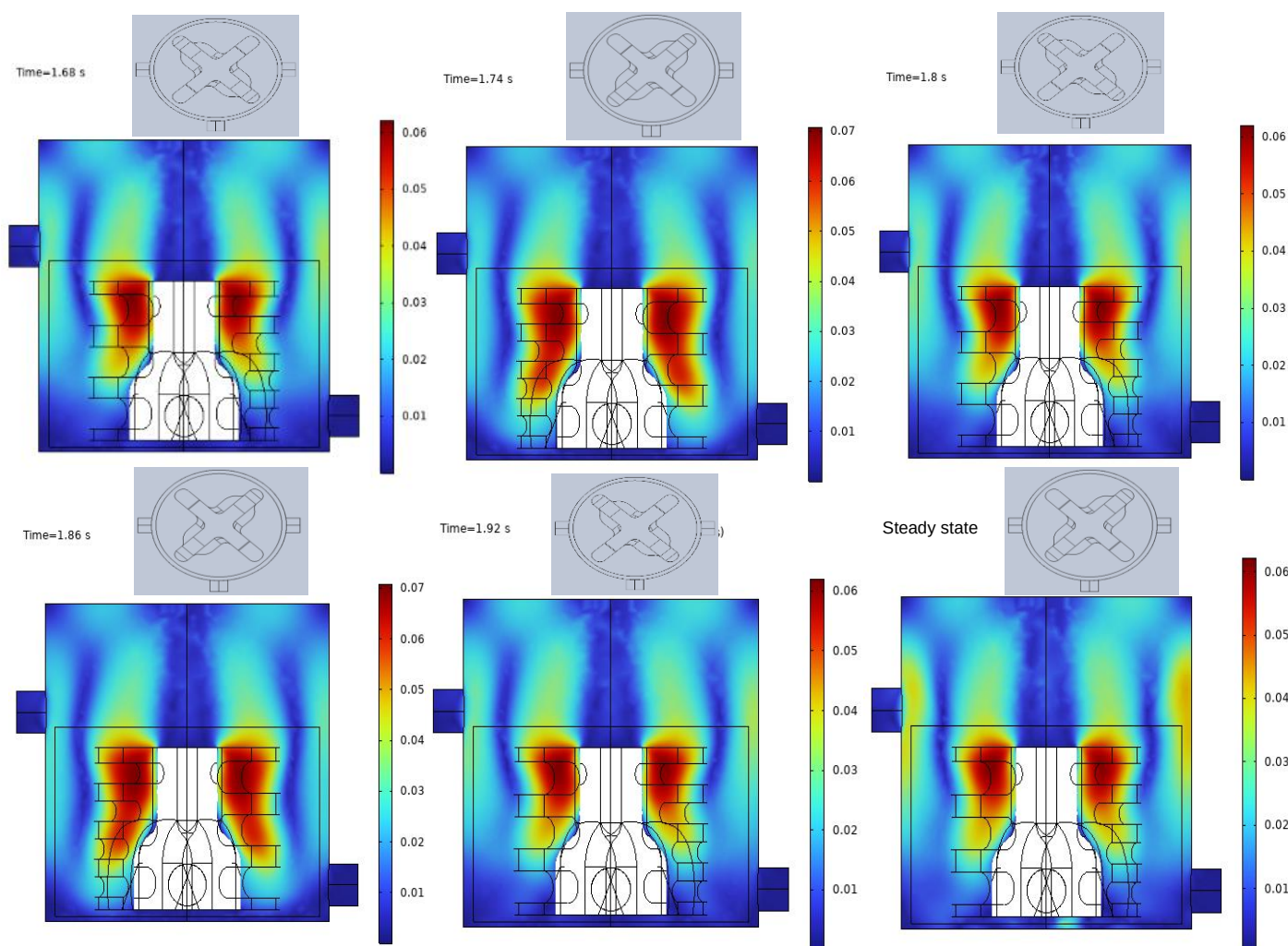


Figure C-9. The velocity contours on a xz plane (plane perpendicular to one inlet and the outlet) of the transient simulation for different timestamps (and impeller angles, respectively), as well as that of the MRF approach. The colour-bars represent the velocity vector magnitude in m/s.

Appendix D. Rapid kinetic parameter estimation via transient experiments in a miniaturised CSTR (SI from Chapter 6)

The experimental data from the transient Q and QT campaigns are reported in Table D-1, Table D-2 and Table D-3 respectively.

Table D-1. Benzaldehyde and *n*-benzylidenebenzylamine average measured concentrations at the reactor outlet from two ramp Q campaigns at 15 °C.

Time (s)	Temperature (°C)	Flowrate (mL/min)	Inlet concentration of benzaldehyde (M)	Average outlet concentration of benzaldehyde (M)	Average outlet concentration of <i>n</i> -benzylidenebenzylamine (M)
0	15.00	4.00	1	0.721	0.229
5	15.00	3.98	1	0.720	0.228
10	15.00	3.96	1	0.719	0.229

15	15.00	3.94	1	0.725	0.230
20	15.00	3.92	1	0.731	0.232
25	15.00	3.90	1	0.717	0.231
30	15.00	3.88	1	0.715	0.232
35	15.00	3.86	1	0.722	0.232
40	15.00	3.84	1	0.715	0.232
45	15.00	3.82	1	0.716	0.232
50	15.00	3.80	1	0.719	0.234
55	15.00	3.78	1	0.718	0.232
60	15.00	3.76	1	0.712	0.233
65	15.00	3.74	1	0.712	0.236
70	15.00	3.72	1	0.724	0.235
75	15.00	3.70	1	0.721	0.236
80	15.00	3.68	1	0.715	0.237
85	15.00	3.66	1	0.719	0.239
90	15.00	3.64	1	0.716	0.238
95	15.00	3.62	1	0.713	0.238
100	15.00	3.60	1	0.719	0.241
105	15.00	3.58	1	0.707	0.239
110	15.00	3.56	1	0.713	0.241
115	15.00	3.54	1	0.710	0.242
120	15.00	3.52	1	0.708	0.243
125	15.00	3.50	1	0.712	0.244
130	15.00	3.48	1	0.709	0.243
135	15.00	3.46	1	0.705	0.243
140	15.00	3.44	1	0.702	0.245
145	15.00	3.42	1	0.709	0.247
150	15.00	3.40	1	0.701	0.246
155	15.00	3.38	1	0.702	0.249
160	15.00	3.36	1	0.703	0.249
165	15.00	3.34	1	0.705	0.250
170	15.00	3.32	1	0.706	0.250
175	15.00	3.30	1	0.703	0.250
180	15.00	3.28	1	0.696	0.251
185	15.00	3.26	1	0.695	0.251
190	15.00	3.24	1	0.702	0.254
195	15.00	3.22	1	0.699	0.254
200	15.00	3.20	1	0.700	0.256
205	15.00	3.18	1	0.690	0.254
210	15.00	3.16	1	0.693	0.258
215	15.00	3.14	1	0.697	0.259
220	15.00	3.12	1	0.687	0.258
225	15.00	3.10	1	0.698	0.259
230	15.00	3.08	1	0.692	0.262

235	15.00	3.06	1	0.695	0.261
240	15.00	3.04	1	0.689	0.262
245	15.00	3.02	1	0.683	0.264
250	15.00	3.00	1	0.697	0.265
255	15.00	2.98	1	0.694	0.265
260	15.00	2.96	1	0.689	0.266
265	15.00	2.94	1	0.687	0.266
270	15.00	2.92	1	0.689	0.268
275	15.00	2.90	1	0.681	0.266
280	15.00	2.88	1	0.675	0.270
285	15.00	2.86	1	0.680	0.270
290	15.00	2.84	1	0.683	0.272
295	15.00	2.82	1	0.675	0.272
300	15.00	2.80	1	0.691	0.273
305	15.00	2.78	1	0.681	0.273
310	15.00	2.76	1	0.681	0.277
315	15.00	2.74	1	0.679	0.277
320	15.00	2.72	1	0.668	0.278
325	15.00	2.70	1	0.674	0.278
330	15.00	2.68	1	0.673	0.280
335	15.00	2.66	1	0.667	0.279
340	15.00	2.64	1	0.671	0.282
345	15.00	2.62	1	0.665	0.282
350	15.00	2.60	1	0.673	0.285
355	15.00	2.58	1	0.671	0.284
360	15.00	2.56	1	0.669	0.287
365	15.00	2.54	1	0.670	0.289
370	15.00	2.52	1	0.666	0.290
375	15.00	2.50	1	0.669	0.289
380	15.00	2.48	1	0.661	0.292
385	15.00	2.46	1	0.667	0.293
390	15.00	2.44	1	0.660	0.293
395	15.00	2.42	1	0.664	0.297
400	15.00	2.40	1	0.667	0.297
405	15.00	2.38	1	0.661	0.299
410	15.00	2.36	1	0.660	0.299
415	15.00	2.34	1	0.662	0.301
420	15.00	2.32	1	0.659	0.303
425	15.00	2.30	1	0.653	0.303
430	15.00	2.28	1	0.659	0.303
435	15.00	2.26	1	0.652	0.304
440	15.00	2.24	1	0.643	0.304
445	15.00	2.22	1	0.649	0.308
450	15.00	2.20	1	0.655	0.312

455	15.00	2.18	1	0.642	0.309
460	15.00	2.16	1	0.652	0.315
465	15.00	2.14	1	0.655	0.318
470	15.00	2.12	1	0.650	0.316
475	15.00	2.10	1	0.641	0.318
480	15.00	2.08	1	0.641	0.318
485	15.00	2.06	1	0.644	0.323
490	15.00	2.04	1	0.641	0.322
495	15.00	2.02	1	0.639	0.323
500	15.00	2.00	1	0.641	0.325
505	15.00	1.98	1	0.644	0.329
510	15.00	1.96	1	0.645	0.330
515	15.00	1.94	1	0.639	0.331
520	15.00	1.92	1	0.644	0.334
525	15.00	1.90	1	0.634	0.334
530	15.00	1.88	1	0.637	0.335
535	15.00	1.86	1	0.617	0.333
540	15.00	1.84	1	0.622	0.336
545	15.00	1.82	1	0.621	0.338
550	15.00	1.80	1	0.620	0.337
555	15.00	1.78	1	0.620	0.344
560	15.00	1.76	1	0.619	0.343
565	15.00	1.74	1	0.625	0.345
570	15.00	1.72	1	0.615	0.344
575	15.00	1.70	1	0.617	0.349
580	15.00	1.68	1	0.612	0.348
585	15.00	1.66	1	0.611	0.353
590	15.00	1.64	1	0.616	0.357
595	15.00	1.62	1	0.608	0.355
600	15.00	1.60	1	0.613	0.358
605	15.00	1.58	1	0.605	0.359
610	15.00	1.56	1	0.608	0.362
615	15.00	1.54	1	0.614	0.366
620	15.00	1.52	1	0.611	0.367
625	15.00	1.50	1	0.604	0.367
630	15.00	1.48	1	0.595	0.369
635	15.00	1.46	1	0.595	0.369
640	15.00	1.44	1	0.594	0.371
645	15.00	1.42	1	0.590	0.373
650	15.00	1.40	1	0.585	0.377
655	15.00	1.38	1	0.590	0.378
660	15.00	1.36	1	0.594	0.382
665	15.00	1.34	1	0.587	0.380
670	15.00	1.32	1	0.582	0.385

675	15.00	1.30	1	0.584	0.386
680	15.00	1.28	1	0.585	0.392
685	15.00	1.26	1	0.571	0.390
690	15.00	1.24	1	0.574	0.390
695	15.00	1.22	1	0.578	0.398
700	15.00	1.20	1	0.574	0.399
705	15.00	1.18	1	0.567	0.397
710	15.00	1.16	1	0.571	0.402
715	15.00	1.14	1	0.575	0.409
720	15.00	1.12	1	0.569	0.410
725	15.00	1.10	1	0.562	0.409
730	15.00	1.08	1	0.563	0.415
735	15.00	1.06	1	0.562	0.418
740	15.00	1.04	1	0.559	0.417
745	15.00	1.02	1	0.552	0.415
750	15.00	1.00	1	0.549	0.420
755	15.00	0.98	1	0.552	0.427
760	15.00	0.96	1	0.541	0.426
765	15.00	0.94	1	0.543	0.432
770	15.00	0.92	1	0.541	0.433
775	15.00	0.90	1	0.546	0.439
780	15.00	0.88	1	0.544	0.439
785	15.00	0.86	1	0.540	0.442
790	15.00	0.84	1	0.536	0.448
795	15.00	0.82	1	0.535	0.450
800	15.00	0.80	1	0.534	0.453
805	15.00	0.78	1	0.523	0.453
810	15.00	0.76	1	0.519	0.460
815	15.00	0.74	1	0.519	0.461
820	15.00	0.72	1	0.509	0.475
825	15.00	0.70	1	0.511	0.464
830	15.00	0.68	1	0.511	0.472
835	15.00	0.66	1	0.508	0.474
840	15.00	0.64	1	0.501	0.476
845	15.00	0.62	1	0.500	0.481
850	15.00	0.60	1	0.491	0.480
855	15.00	0.58	1	0.498	0.487
860	15.00	0.56	1	0.490	0.489
865	15.00	0.54	1	0.491	0.491
870	15.00	0.52	1	0.489	0.498
875	15.00	0.50	1	0.477	0.497
880	15.00	0.48	1	0.485	0.506
885	15.00	0.46	1	0.481	0.507
890	15.00	0.44	1	0.469	0.510

895	15.00	0.42	1	0.473	0.517
900	15.00	0.40	1	0.470	0.522
905	15.00	0.38	1	0.467	0.528
910	15.00	0.36	1	0.459	0.527
915	15.00	0.34	1	0.457	0.532
920	15.00	0.32	1	0.453	0.537
925	15.00	0.30	1	0.453	0.542
930	15.00	0.28	1	0.444	0.544
935	15.00	0.26	1	0.444	0.549
940	15.00	0.24	1	0.440	0.558
945	15.00	0.22	1	0.425	0.555
950	15.00	0.20	1	0.434	0.564
955	15.00	0.18	1	0.427	0.568
960	15.00	0.16	1	0.424	0.572
965	15.00	0.14	1	0.420	0.578
970	15.00	0.12	1	0.406	0.582
975	15.00	0.10	1	0.408	0.591

Table D-2. Benzaldehyde and *n*-benzylidenebenzylamine average measured concentrations at the reactor outlet from two ramp Q campaigns at 45 °C.

Time (s)	Temperature (°C)	Flowrate (mL/min)	Inlet concentration of benzaldehyde (M)	Average outlet concentration of benzaldehyde (M)	Average outlet concentration of <i>n</i> -benzylidenebenzylamine (M)
0	45.00	4.00	1	0.585	0.405
5	45.00	3.98	1	0.584	0.405
10	45.00	3.96	1	0.580	0.407
15	45.00	3.94	1	0.587	0.406
20	45.00	3.92	1	0.585	0.411
25	45.00	3.90	1	0.574	0.406
30	45.00	3.88	1	0.565	0.405
35	45.00	3.86	1	0.583	0.410
40	45.00	3.84	1	0.574	0.410
45	45.00	3.82	1	0.575	0.410
50	45.00	3.80	1	0.572	0.410
55	45.00	3.78	1	0.581	0.414
60	45.00	3.76	1	0.581	0.414
65	45.00	3.74	1	0.572	0.416
70	45.00	3.72	1	0.575	0.417
75	45.00	3.70	1	0.573	0.414
80	45.00	3.68	1	0.567	0.418
85	45.00	3.66	1	0.563	0.419
90	45.00	3.64	1	0.560	0.420

95	45.00	3.62	1	0.557	0.418
100	45.00	3.60	1	0.559	0.418
105	45.00	3.58	1	0.567	0.417
110	45.00	3.56	1	0.565	0.421
115	45.00	3.54	1	0.566	0.419
120	45.00	3.52	1	0.556	0.423
125	45.00	3.50	1	0.545	0.424
130	45.00	3.48	1	0.559	0.423
135	45.00	3.46	1	0.558	0.425
140	45.00	3.44	1	0.561	0.426
145	45.00	3.42	1	0.554	0.430
150	45.00	3.40	1	0.563	0.430
155	45.00	3.38	1	0.552	0.433
160	45.00	3.36	1	0.549	0.433
165	45.00	3.34	1	0.557	0.433
170	45.00	3.32	1	0.550	0.436
175	45.00	3.30	1	0.541	0.433
180	45.00	3.28	1	0.539	0.434
185	45.00	3.26	1	0.547	0.438
190	45.00	3.24	1	0.551	0.440
195	45.00	3.22	1	0.545	0.438
200	45.00	3.20	1	0.535	0.437
205	45.00	3.18	1	0.540	0.438
210	45.00	3.16	1	0.545	0.439
215	45.00	3.14	1	0.540	0.444
220	45.00	3.12	1	0.530	0.442
225	45.00	3.10	1	0.534	0.442
230	45.00	3.08	1	0.540	0.447
235	45.00	3.06	1	0.537	0.450
240	45.00	3.04	1	0.534	0.446
245	45.00	3.02	1	0.536	0.448
250	45.00	3.00	1	0.532	0.452
255	45.00	2.98	1	0.534	0.452
260	45.00	2.96	1	0.532	0.454
265	45.00	2.94	1	0.533	0.455
270	45.00	2.92	1	0.529	0.453
275	45.00	2.90	1	0.527	0.454
280	45.00	2.88	1	0.530	0.458
285	45.00	2.86	1	0.529	0.459
290	45.00	2.84	1	0.514	0.458
295	45.00	2.82	1	0.523	0.459
300	45.00	2.80	1	0.519	0.459
305	45.00	2.78	1	0.528	0.461
310	45.00	2.76	1	0.516	0.466

315	45.00	2.74	1	0.519	0.463
320	45.00	2.72	1	0.519	0.469
325	45.00	2.70	1	0.512	0.464
330	45.00	2.68	1	0.511	0.467
335	45.00	2.66	1	0.511	0.472
340	45.00	2.64	1	0.512	0.474
345	45.00	2.62	1	0.516	0.473
350	45.00	2.60	1	0.510	0.476
355	45.00	2.58	1	0.507	0.475
360	45.00	2.56	1	0.498	0.474
365	45.00	2.54	1	0.502	0.475
370	45.00	2.52	1	0.500	0.481
375	45.00	2.50	1	0.500	0.478
380	45.00	2.48	1	0.500	0.480
385	45.00	2.46	1	0.501	0.480
390	45.00	2.44	1	0.500	0.484
395	45.00	2.42	1	0.495	0.488
400	45.00	2.40	1	0.495	0.486
405	45.00	2.38	1	0.492	0.485
410	45.00	2.36	1	0.490	0.489
415	45.00	2.34	1	0.494	0.487
420	45.00	2.32	1	0.494	0.493
425	45.00	2.30	1	0.481	0.491
430	45.00	2.28	1	0.490	0.495
435	45.00	2.26	1	0.484	0.494
440	45.00	2.24	1	0.479	0.494
445	45.00	2.22	1	0.483	0.497
450	45.00	2.20	1	0.486	0.500
455	45.00	2.18	1	0.479	0.499
460	45.00	2.16	1	0.479	0.501
465	45.00	2.14	1	0.478	0.502
470	45.00	2.12	1	0.470	0.504
475	45.00	2.10	1	0.471	0.505
480	45.00	2.08	1	0.476	0.508
485	45.00	2.06	1	0.474	0.512
490	45.00	2.04	1	0.472	0.512
495	45.00	2.02	1	0.466	0.510
500	45.00	2.00	1	0.473	0.515
505	45.00	1.98	1	0.467	0.516
510	45.00	1.96	1	0.462	0.517
515	45.00	1.94	1	0.461	0.517
520	45.00	1.92	1	0.460	0.517
525	45.00	1.90	1	0.461	0.526
530	45.00	1.88	1	0.454	0.521

535	45.00	1.86	1	0.454	0.524
540	45.00	1.84	1	0.458	0.527
545	45.00	1.82	1	0.448	0.529
550	45.00	1.80	1	0.452	0.531
555	45.00	1.78	1	0.446	0.534
560	45.00	1.76	1	0.443	0.533
565	45.00	1.74	1	0.448	0.539
570	45.00	1.72	1	0.437	0.535
575	45.00	1.70	1	0.440	0.538
580	45.00	1.68	1	0.434	0.537
585	45.00	1.66	1	0.438	0.543
590	45.00	1.64	1	0.437	0.542
595	45.00	1.62	1	0.436	0.545
600	45.00	1.60	1	0.432	0.546
605	45.00	1.58	1	0.418	0.547
610	45.00	1.56	1	0.425	0.551
615	45.00	1.54	1	0.427	0.553
620	45.00	1.52	1	0.424	0.554
625	45.00	1.50	1	0.418	0.554
630	45.00	1.48	1	0.417	0.560
635	45.00	1.46	1	0.423	0.562
640	45.00	1.44	1	0.417	0.564
645	45.00	1.42	1	0.422	0.566
650	45.00	1.40	1	0.410	0.564
655	45.00	1.38	1	0.410	0.561
660	45.00	1.36	1	0.412	0.572
665	45.00	1.34	1	0.409	0.573
670	45.00	1.32	1	0.407	0.576
675	45.00	1.30	1	0.412	0.578
680	45.00	1.28	1	0.400	0.584
685	45.00	1.26	1	0.409	0.583
690	45.00	1.24	1	0.396	0.579
695	45.00	1.22	1	0.394	0.582
700	45.00	1.20	1	0.393	0.585
705	45.00	1.18	1	0.395	0.584
710	45.00	1.16	1	0.387	0.588
715	45.00	1.14	1	0.385	0.591
720	45.00	1.12	1	0.389	0.596
725	45.00	1.10	1	0.384	0.597
730	45.00	1.08	1	0.385	0.597
735	45.00	1.06	1	0.385	0.602
740	45.00	1.04	1	0.374	0.603
745	45.00	1.02	1	0.378	0.607
750	45.00	1.00	1	0.375	0.611

755	45.00	0.98	1	0.369	0.610
760	45.00	0.96	1	0.371	0.615
765	45.00	0.94	1	0.365	0.615
770	45.00	0.92	1	0.364	0.616
775	45.00	0.90	1	0.361	0.621
780	45.00	0.88	1	0.361	0.623
785	45.00	0.86	1	0.360	0.625
790	45.00	0.84	1	0.348	0.628
795	45.00	0.82	1	0.354	0.632
800	45.00	0.80	1	0.354	0.629
805	45.00	0.78	1	0.348	0.636
810	45.00	0.76	1	0.346	0.641
815	45.00	0.74	1	0.345	0.638
820	45.00	0.72	1	0.335	0.642
825	45.00	0.70	1	0.339	0.646
830	45.00	0.68	1	0.331	0.646
835	45.00	0.66	1	0.330	0.654
840	45.00	0.64	1	0.326	0.651
845	45.00	0.62	1	0.330	0.648
850	45.00	0.60	1	0.326	0.663
855	45.00	0.58	1	0.318	0.660
860	45.00	0.56	1	0.321	0.668
865	45.00	0.54	1	0.312	0.665
870	45.00	0.52	1	0.309	0.671
875	45.00	0.50	1	0.312	0.675
880	45.00	0.48	1	0.305	0.677
885	45.00	0.46	1	0.304	0.683
890	45.00	0.44	1	0.291	0.681
895	45.00	0.42	1	0.293	0.686
900	45.00	0.40	1	0.298	0.691
905	45.00	0.38	1	0.289	0.693
910	45.00	0.36	1	0.286	0.699
915	45.00	0.34	1	0.281	0.700
920	45.00	0.32	1	0.282	0.705
925	45.00	0.30	1	0.275	0.706
930	45.00	0.28	1	0.269	0.710
935	45.00	0.26	1	0.267	0.713
940	45.00	0.24	1	0.265	0.723
945	45.00	0.22	1	0.264	0.724
950	45.00	0.20	1	0.261	0.728
955	45.00	0.18	1	0.254	0.731
960	45.00	0.16	1	0.257	0.734
965	45.00	0.14	1	0.253	0.741
970	45.00	0.12	1	0.245	0.745

975	45.00	0.10	1	0.235	0.745
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Table D-3. Benzaldehyde and benzylamine average measured concentration at the reactor outlet from three ramp QT campaigns.

Time (s)	Temperature (°C)	Flowrate (mL/min)	Inlet concentration of benzaldehyde (M)	Average outlet concentration of benzaldehyde (M)	Average outlet concentration of n-benzilydenebenzylamine (M)
0	15.00	2.000	1	0.644	0.370
5	15.08	1.996	1	0.657	0.374
10	15.17	1.992	1	0.659	0.375
15	15.25	1.987	1	0.656	0.377
20	15.33	1.983	1	0.647	0.377
25	15.42	1.979	1	0.650	0.378
30	15.50	1.975	1	0.665	0.381
35	15.58	1.971	1	0.657	0.380
40	15.67	1.967	1	0.660	0.378
45	15.75	1.962	1	0.659	0.381
50	15.83	1.958	1	0.658	0.382
55	15.92	1.954	1	0.651	0.382
60	16.00	1.950	1	0.659	0.387
65	16.08	1.946	1	0.660	0.385
70	16.17	1.942	1	0.653	0.386
75	16.25	1.937	1	0.660	0.387
80	16.33	1.933	1	0.656	0.387
85	16.42	1.929	1	0.655	0.390
90	16.50	1.925	1	0.651	0.388
95	16.58	1.921	1	0.658	0.390
100	16.67	1.917	1	0.647	0.393
105	16.75	1.912	1	0.650	0.392
110	16.83	1.908	1	0.655	0.393
115	16.92	1.904	1	0.648	0.395
120	17.00	1.900	1	0.654	0.397
125	17.08	1.896	1	0.640	0.397
130	17.17	1.892	1	0.648	0.399
135	17.25	1.887	1	0.644	0.398
140	17.33	1.883	1	0.640	0.403
145	17.42	1.879	1	0.639	0.397
150	17.50	1.875	1	0.627	0.396
155	17.58	1.871	1	0.622	0.399
160	17.67	1.867	1	0.628	0.401
165	17.75	1.862	1	0.629	0.405
170	17.83	1.858	1	0.631	0.404

175	17.92	1.854	1	0.625	0.406
180	18.00	1.850	1	0.627	0.409
185	18.08	1.846	1	0.630	0.410
190	18.17	1.842	1	0.624	0.411
195	18.25	1.837	1	0.625	0.416
200	18.33	1.833	1	0.618	0.411
205	18.42	1.829	1	0.619	0.413
210	18.50	1.825	1	0.614	0.415
215	18.58	1.821	1	0.608	0.412
220	18.67	1.817	1	0.612	0.415
225	18.75	1.812	1	0.610	0.417
230	18.83	1.808	1	0.602	0.420
235	18.92	1.804	1	0.613	0.420
240	19.00	1.800	1	0.614	0.423
245	19.08	1.796	1	0.609	0.421
250	19.17	1.792	1	0.609	0.423
255	19.25	1.787	1	0.614	0.425
260	19.33	1.783	1	0.611	0.427
265	19.42	1.779	1	0.614	0.427
270	19.50	1.775	1	0.610	0.429
275	19.58	1.771	1	0.607	0.431
280	19.67	1.767	1	0.609	0.433
285	19.75	1.762	1	0.605	0.436
290	19.83	1.758	1	0.611	0.438
295	19.92	1.754	1	0.609	0.437
300	20.00	1.750	1	0.606	0.437
305	20.08	1.746	1	0.599	0.440
310	20.17	1.742	1	0.609	0.442
315	20.25	1.737	1	0.609	0.443
320	20.33	1.733	1	0.603	0.444
325	20.42	1.729	1	0.604	0.448
330	20.50	1.725	1	0.604	0.451
335	20.58	1.721	1	0.598	0.449
340	20.67	1.717	1	0.601	0.450
345	20.75	1.712	1	0.601	0.453
350	20.83	1.708	1	0.602	0.453
355	20.92	1.704	1	0.598	0.452
360	21.00	1.700	1	0.591	0.457
365	21.08	1.696	1	0.592	0.456
370	21.17	1.692	1	0.593	0.455
375	21.25	1.687	1	0.586	0.457
380	21.33	1.683	1	0.590	0.460
385	21.42	1.679	1	0.589	0.460
390	21.50	1.675	1	0.588	0.466

395	21.58	1.671	1	0.588	0.464
400	21.67	1.667	1	0.589	0.466
405	21.75	1.662	1	0.589	0.466
410	21.83	1.658	1	0.582	0.466
415	21.92	1.654	1	0.579	0.469
420	22.00	1.650	1	0.584	0.468
425	22.08	1.646	1	0.582	0.472
430	22.17	1.642	1	0.577	0.474
435	22.25	1.637	1	0.580	0.469
440	22.33	1.633	1	0.576	0.473
445	22.42	1.629	1	0.579	0.476
450	22.50	1.625	1	0.576	0.480
455	22.58	1.621	1	0.573	0.476
460	22.67	1.617	1	0.572	0.479
465	22.75	1.612	1	0.568	0.479
470	22.83	1.608	1	0.568	0.478
475	22.92	1.604	1	0.568	0.481
480	23.00	1.600	1	0.563	0.484
485	23.08	1.596	1	0.568	0.485
490	23.17	1.592	1	0.567	0.486
495	23.25	1.587	1	0.566	0.488
500	23.33	1.583	1	0.559	0.486
505	23.42	1.579	1	0.559	0.490
510	23.50	1.575	1	0.561	0.488
515	23.58	1.571	1	0.563	0.493
520	23.67	1.567	1	0.557	0.492
525	23.75	1.562	1	0.558	0.492
530	23.83	1.558	1	0.545	0.497
535	23.92	1.554	1	0.556	0.496
540	24.00	1.550	1	0.552	0.499
545	24.08	1.546	1	0.546	0.499
550	24.17	1.542	1	0.549	0.501
555	24.25	1.537	1	0.546	0.502
560	24.33	1.533	1	0.552	0.505
565	24.42	1.529	1	0.539	0.501
570	24.50	1.525	1	0.545	0.503
575	24.58	1.521	1	0.551	0.502
580	24.67	1.517	1	0.538	0.501
585	24.75	1.512	1	0.539	0.503
590	24.83	1.508	1	0.535	0.506
595	24.92	1.504	1	0.540	0.508
600	25.00	1.500	1	0.544	0.507
605	25.08	1.496	1	0.539	0.508
610	25.17	1.492	1	0.539	0.506

615	25.25	1.487	1	0.539	0.509
620	25.33	1.483	1	0.536	0.514
625	25.42	1.479	1	0.537	0.512
630	25.50	1.475	1	0.532	0.512
635	25.58	1.471	1	0.533	0.518
640	25.67	1.467	1	0.533	0.516
645	25.75	1.462	1	0.524	0.517
650	25.83	1.458	1	0.527	0.518
655	25.92	1.454	1	0.529	0.521
660	26.00	1.450	1	0.528	0.521
665	26.08	1.446	1	0.527	0.525
670	26.17	1.442	1	0.529	0.525
675	26.25	1.437	1	0.521	0.522
680	26.33	1.433	1	0.520	0.522
685	26.42	1.429	1	0.514	0.525
690	26.50	1.425	1	0.509	0.528
695	26.58	1.421	1	0.513	0.525
700	26.67	1.417	1	0.508	0.524
705	26.75	1.412	1	0.515	0.528
710	26.83	1.408	1	0.509	0.530
715	26.92	1.404	1	0.508	0.526
720	27.00	1.400	1	0.508	0.529
725	27.08	1.396	1	0.501	0.535
730	27.17	1.392	1	0.500	0.535
735	27.25	1.387	1	0.507	0.534
740	27.33	1.383	1	0.502	0.535
745	27.42	1.379	1	0.501	0.537
750	27.50	1.375	1	0.497	0.540
755	27.58	1.371	1	0.498	0.541
760	27.67	1.367	1	0.500	0.539
765	27.75	1.362	1	0.491	0.540
770	27.83	1.358	1	0.494	0.545
775	27.92	1.354	1	0.494	0.547
780	28.00	1.350	1	0.495	0.548
785	28.08	1.346	1	0.499	0.551
790	28.17	1.342	1	0.496	0.552
795	28.25	1.337	1	0.483	0.551
800	28.33	1.333	1	0.494	0.555
805	28.42	1.329	1	0.489	0.556
810	28.50	1.325	1	0.488	0.561
815	28.58	1.321	1	0.495	0.560
820	28.67	1.317	1	0.483	0.560
825	28.75	1.312	1	0.481	0.559
830	28.83	1.308	1	0.486	0.563

835	28.92	1.304	1	0.481	0.562
840	29.00	1.300	1	0.484	0.562
845	29.08	1.296	1	0.486	0.565
850	29.17	1.292	1	0.478	0.566
855	29.25	1.287	1	0.476	0.566
860	29.33	1.283	1	0.471	0.569
865	29.42	1.279	1	0.479	0.567
870	29.50	1.275	1	0.478	0.568
875	29.58	1.271	1	0.474	0.565
880	29.67	1.267	1	0.478	0.569
885	29.75	1.262	1	0.469	0.570
890	29.83	1.258	1	0.466	0.571
895	29.92	1.254	1	0.468	0.574
900	30.00	1.250	1	0.468	0.572
905	30.08	1.246	1	0.466	0.573
910	30.17	1.242	1	0.459	0.571
915	30.25	1.237	1	0.461	0.573
920	30.33	1.233	1	0.457	0.574
925	30.42	1.229	1	0.455	0.576
930	30.50	1.225	1	0.454	0.578
935	30.58	1.221	1	0.455	0.579
940	30.67	1.217	1	0.453	0.577
945	30.75	1.212	1	0.452	0.584
950	30.83	1.208	1	0.450	0.580
955	30.92	1.204	1	0.447	0.581
960	31.00	1.200	1	0.454	0.582
965	31.08	1.196	1	0.454	0.585
970	31.17	1.192	1	0.457	0.586
975	31.25	1.187	1	0.449	0.585
980	31.33	1.183	1	0.450	0.588
985	31.42	1.179	1	0.443	0.588
990	31.50	1.175	1	0.445	0.594
995	31.58	1.171	1	0.449	0.593
1000	31.67	1.167	1	0.446	0.598
1005	31.75	1.162	1	0.438	0.591
1010	31.83	1.158	1	0.432	0.591
1015	31.92	1.154	1	0.433	0.592
1020	32.00	1.150	1	0.436	0.595
1025	32.08	1.146	1	0.436	0.596
1030	32.17	1.142	1	0.430	0.597
1035	32.25	1.137	1	0.433	0.594
1040	32.33	1.133	1	0.432	0.598
1045	32.42	1.129	1	0.421	0.598
1050	32.50	1.125	1	0.428	0.601

1055	32.58	1.121	1	0.422	0.601
1060	32.67	1.117	1	0.424	0.597
1065	32.75	1.112	1	0.422	0.599
1070	32.83	1.108	1	0.426	0.601
1075	32.92	1.104	1	0.418	0.604
1080	33.00	1.100	1	0.424	0.604
1085	33.08	1.096	1	0.423	0.602
1090	33.17	1.092	1	0.417	0.608
1095	33.25	1.087	1	0.413	0.611
1100	33.33	1.083	1	0.417	0.611
1105	33.42	1.079	1	0.419	0.609
1110	33.50	1.075	1	0.410	0.612
1115	33.58	1.071	1	0.414	0.614
1120	33.67	1.067	1	0.408	0.609
1125	33.75	1.062	1	0.414	0.615
1130	33.83	1.058	1	0.409	0.617
1135	33.92	1.054	1	0.408	0.619
1140	34.00	1.050	1	0.402	0.619
1145	34.08	1.046	1	0.404	0.619
1150	34.17	1.042	1	0.401	0.616
1155	34.25	1.037	1	0.402	0.619
1160	34.33	1.033	1	0.397	0.625
1165	34.42	1.029	1	0.402	0.623
1170	34.50	1.025	1	0.402	0.624
1175	34.58	1.021	1	0.395	0.625
1180	34.67	1.017	1	0.404	0.624
1185	34.75	1.012	1	0.402	0.629
1190	34.83	1.008	1	0.395	0.631
1195	34.92	1.004	1	0.396	0.630
1200	35.00	1.000	1	0.395	0.629
1205	35.08	0.996	1	0.393	0.630
1210	35.17	0.992	1	0.395	0.632
1215	35.25	0.987	1	0.388	0.635
1220	35.33	0.983	1	0.391	0.634
1225	35.42	0.979	1	0.392	0.638
1230	35.50	0.975	1	0.390	0.643
1235	35.58	0.971	1	0.394	0.646
1240	35.67	0.967	1	0.388	0.642
1245	35.75	0.962	1	0.392	0.645
1250	35.83	0.958	1	0.393	0.649
1255	35.92	0.954	1	0.383	0.645
1260	36.00	0.950	1	0.380	0.643
1265	36.08	0.946	1	0.379	0.646
1270	36.17	0.942	1	0.389	0.647

1275	36.25	0.937	1	0.379	0.646
1280	36.33	0.933	1	0.378	0.643
1285	36.42	0.929	1	0.373	0.645
1290	36.50	0.925	1	0.374	0.645
1295	36.58	0.921	1	0.375	0.647
1300	36.67	0.917	1	0.370	0.652
1305	36.75	0.912	1	0.367	0.647
1310	36.83	0.908	1	0.375	0.653
1315	36.92	0.904	1	0.370	0.650
1320	37.00	0.900	1	0.365	0.649
1325	37.08	0.896	1	0.367	0.650
1330	37.17	0.892	1	0.365	0.648
1335	37.25	0.887	1	0.361	0.648
1340	37.33	0.883	1	0.361	0.650
1345	37.42	0.879	1	0.360	0.653
1350	37.50	0.875	1	0.356	0.652
1355	37.58	0.871	1	0.359	0.658
1360	37.67	0.867	1	0.355	0.660
1365	37.75	0.862	1	0.356	0.657
1370	37.83	0.858	1	0.358	0.660
1375	37.92	0.854	1	0.353	0.662
1380	38.00	0.850	1	0.352	0.664
1385	38.08	0.846	1	0.356	0.670
1390	38.17	0.842	1	0.345	0.666
1395	38.25	0.837	1	0.355	0.668
1400	38.33	0.833	1	0.352	0.673
1405	38.42	0.829	1	0.345	0.672
1410	38.50	0.825	1	0.354	0.673
1415	38.58	0.821	1	0.344	0.674
1420	38.67	0.817	1	0.351	0.680
1425	38.75	0.812	1	0.345	0.677
1430	38.83	0.808	1	0.340	0.675
1435	38.92	0.804	1	0.341	0.676
1440	39.00	0.800	1	0.338	0.677
1445	39.08	0.796	1	0.346	0.683
1450	39.17	0.792	1	0.335	0.676
1455	39.25	0.787	1	0.339	0.678
1460	39.33	0.783	1	0.337	0.680
1465	39.42	0.779	1	0.337	0.681
1470	39.50	0.775	1	0.343	0.683
1475	39.58	0.771	1	0.336	0.680
1480	39.67	0.767	1	0.327	0.681
1485	39.75	0.762	1	0.326	0.684
1490	39.83	0.758	1	0.331	0.685

Appendix E. Preliminary studies using FTIR microscopy for liquid-phase reactors

In this thesis, the spectroscopic technique of choice for acquiring reaction kinetic data was Raman spectroscopy. However, as extensively deliberated in Section 2.2, an alternative reliable method for rapid, non-destructive quantitative analysis is IR spectroscopy. When performing analysis with FTIR spectroscopy, the spectra of the sample can be practically measured in transmission or reflection. Reflection methods can be divided in two main categories: external reflectance techniques and internal reflectance, widely known as Attenuated Total Reflectance (ATR) [211]. ATR is the most reported IR technique in kinetic studies involving micro-reactors, with measurements typically conducted at the outlet of the reactor, via either a flow-through cell [67], such as the ReactIR flowcell [215-217], or by using the surface of the crystal itself to form on side of the microfluidic device [178, 210, 218]. The preference for ATR over in-situ FTIR in transmission [195] or traditional reflection modes [196], stems from the challenges associated with reactor fabrication (geometry and material) and the interaction between the IR beam and the sample [209].

Concerning the reactor material, conventional FTIR window materials like KBr and CaF_2 may not be compatible with various reagents/products and their brittle nature poses challenges for microfabrication. Silicon, on the other hand, which offers the advantage of IR transparency across much of the spectral range of interest ($4000\text{--}1000\text{ cm}^{-1}$), high thermal conductivity [488] and chemical inertness [489] hinders visual inspection due to its opacity.

To comprehend the limitations arising from the interaction of the infrared (IR) beam with the sample in transmission and external reflectance modes, specifically specular reflectance and transmission-reflectance, it is imperative to delve into the fundamental principles of these techniques.

In transmission mode, the incident radiation penetrates directly into the sample, where specific wavelengths or frequencies of light are absorbed. The frequencies not absorbed are transmitted to the detector, provided that the sample thickness is sufficient to allow the passage of light within the desired range of frequencies.

Specular reflectance techniques involve a mirror-like reflection from the sample surface, occurring when the angle of reflection equals the angle of incidence. In transmission-reflection (transflectance) measurements, wherein the sample is deposited on a reflective surface, a fraction of the radiation is reflected at the upper interface contributing to the spectrum via specular reflection. Another portion of the radiation penetrates the surface film and undergoes reflection by the reflective surface. Consequently, the light traverses the surface layer twice,

once towards and once from the reflective surface, resulting in an increased intensity of the reflectance spectrum compared to normal transmission [490].

To ensure acquisition of Fourier-transform infrared (FTIR) spectra with a favourable signal-to-noise ratio (SNR), it is crucial that the IR beam is either detected after passing through the filled channel in transmission mode or reflected on a surface without significant scattering in transreflectance mode. Hence, constraints on channel depth, necessary for obtaining spectra with satisfactory SNR, lead to notable pressure gradients. This limitation arises from the absorption characteristics exhibited by numerous solvents, notably water and suspensions, which constrain the effective path length for incident IR radiation within the solution.

Figure E-1 provides a visual representation of these different methods for clarity, with focus on employing FTIR microscopy that combines conventional light microscopy with FTIR spectroscopy, thus allowing for the analysis of chemical composition and molecular structure of materials on a microscopic scale [491].

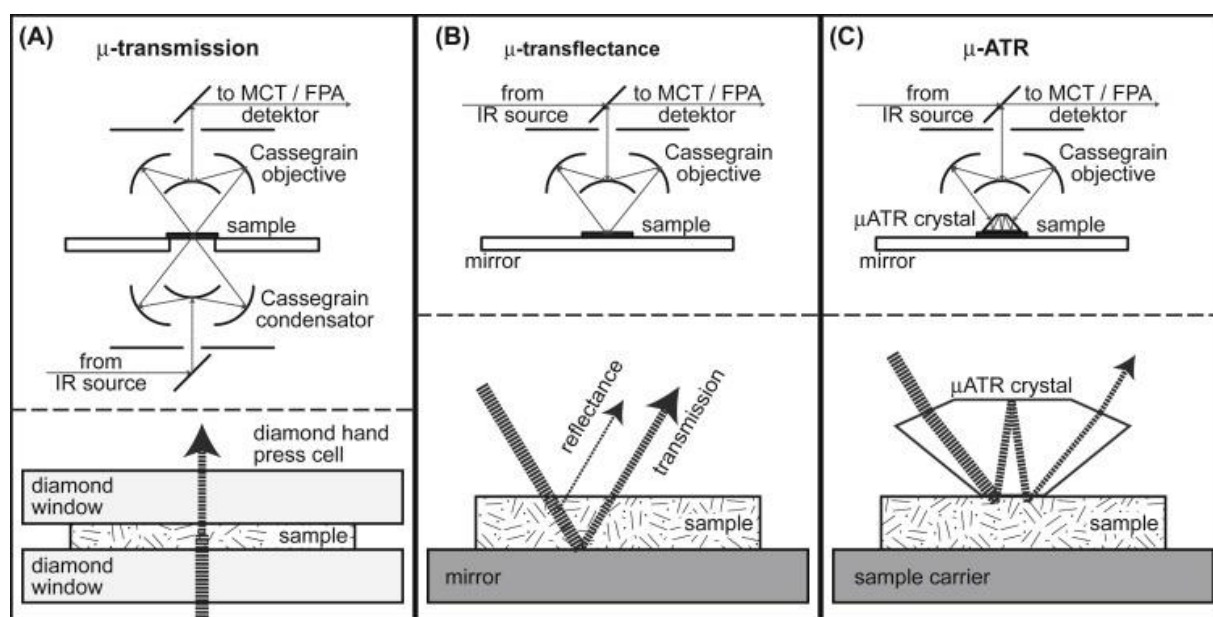


Figure E-1. Overview of FTIR microscopy techniques. (a) Transmission, (b) Transflectance and (c) ATR (adapted from [491] with permission from the publisher).

FTIR micro-reflectance measurements have been primarily conducted on solid materials, ranging from the quantitative analysis of volatile species (H_2O , CO_2 , S-bearing species, etc.) in silicate glasses [492-494] to the detection of microplastics [495]. Typically, substrates with excellent reflective properties, such as gold or aluminium, are employed in these experiments. Given that the m-CSTR introduced in Chapter 5 is fabricated from stainless steel, which inherently possesses reflective properties, the objective was to investigate the feasibility of acquiring IR spectra of known compounds in-situ within the reactor using an FTIR microscope (AIM-9000, Shimadzu) in transreflectance mode. Considering the relatively deep reactor

chamber of the m-CSTR (15 mm depth), an initial evaluation was carried out using a simpler and shallower prototype (8.5 mm depth, 1.5 mL), made of aluminium. Aluminium, with its reduced cost compared to stainless steel, also serves as a reflective surface in the infrared spectral range [496]. The CAD design and real-life prototype of this preliminary setup are illustrated in Figure E-2. To ensure compatibility with different spectroscopic techniques, the reactor window was changed from quartz to CaF_2 , maintaining identical thickness and diameter, highlighting the adaptable nature of the design. Additionally, to facilitate efficient mixing within the chamber while accommodating the space available between the IR lenses and the microscope stage, the reactor was mounted on an ultra-flat magnetic stirring plate (Medline Scientific).

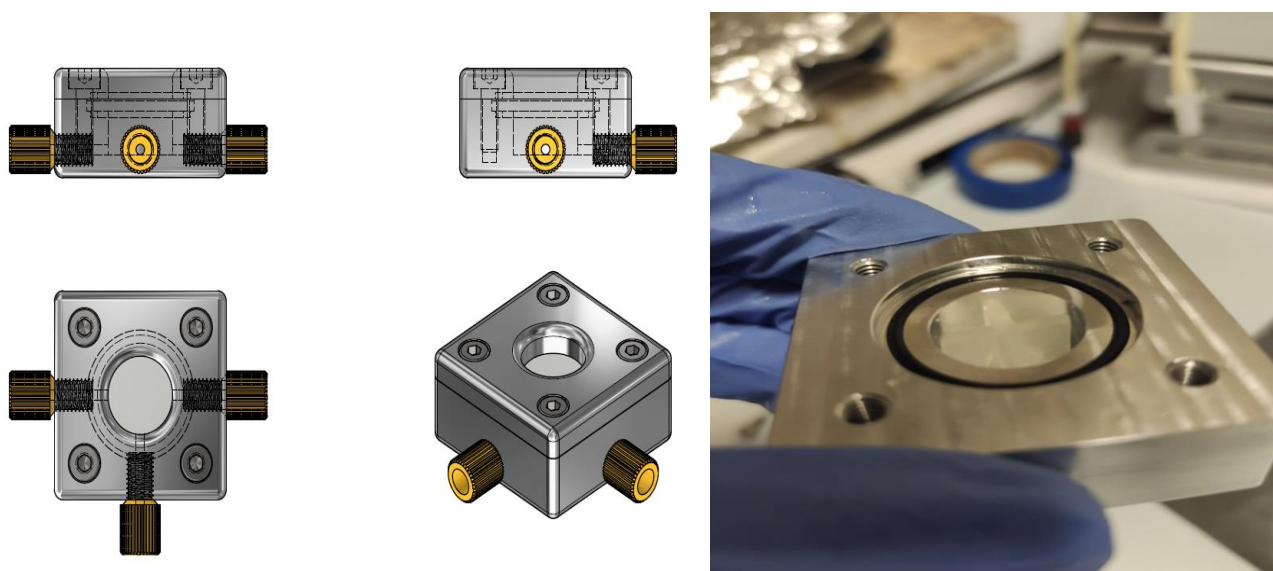


Figure E-2. CAD design in Fusion 360 (left) and real-life prototype (right) of a simplified aluminium version of the m-CSTR introduced in Chapter 5, with reactor diameter of 15 mm and depth of 8.5 mm (total volume of 1.5 mL).

The signal acquisition procedure followed can be summarized in the following steps:

- 1) After mounting the empty reactor on the stage, a background scan at a specific focal depth, using a fixed aperture, was conducted.
- 2) The reactor was, then, filled with the substance of interest, ensuring no air was trapped that could interfere with the signal. A sample scan inside the reactor chamber, at the same focal depth as the previously recorded background, was performed.

The aperture selected was $50\ \mu\text{m}$, the spectral resolution was set at $8\ \text{cm}^{-1}$ and the average spectra collected for every measurement was 50, to ensure a sufficiently high signal intensity, while retaining the ability to resolve narrower peaks. Pure levulinic acid (98%, Sigma Aldrich), was chosen as the compound to be first investigated. In Figure E-3, the spectra of LA measured using a FTIR spectrometer (Bruker ALPHA) with a diamond ATR accessory

(Specac, Quest Single Reflection ATR)⁷ (Figure E-3a) and the FTIR microscope (AIM 9000, Shimadzu) in reflection mode (Figure E-3b) are depicted. It is apparent that, although the spectrum produced by transmittance had a lower SNR compared the ATR measurement, all significant peaks were identified. In detail, a sharp peak at 1700 cm^{-1} that corresponds to the stretching vibrations of the carbonyl (C=O) functional group was observed in both spectra, followed by the two CH_3 bend peaks between 1350 cm^{-1} and 1400 cm^{-1} and the strong stretching vibrations of hydroxyl (OH) groups that contributed to the peak at 1158 cm^{-1} .

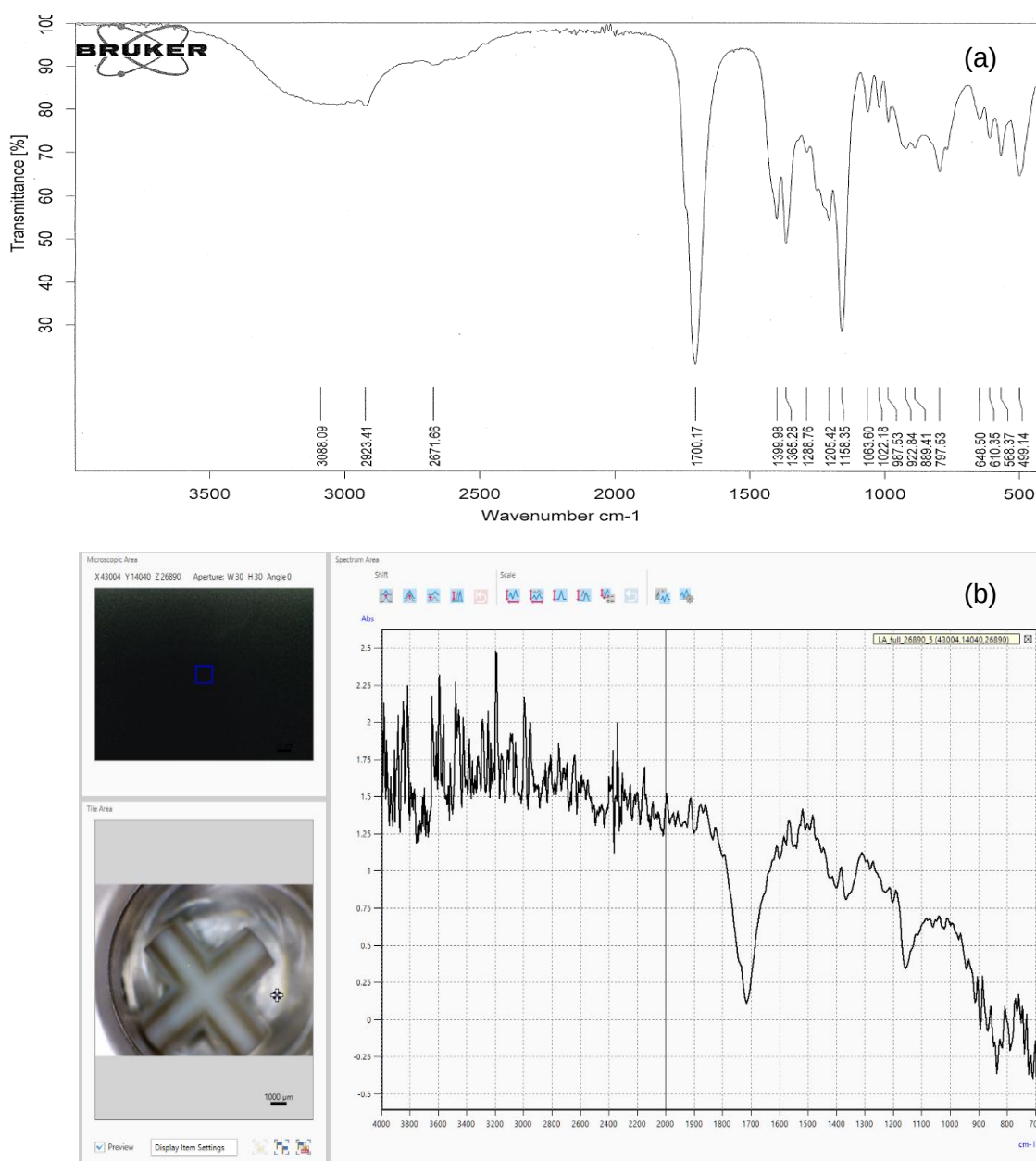


Figure E-3. IR spectrum of levulinic acid and identification of its main peaks, as measured in (a) ATR mode using an FTIR spectrometer (ALPHA Bruker) with a diamond crystal (Specac) and (b) in transmittance mode under the FTIR Microscope (Shimadzu).

⁷ The ATR measurements were performed by Mr. Martyn Towner from the Department of Chemistry at UCL.

At this juncture, it is crucial to emphasize that the units of the y-axis, whether displaying transmittance or absorbance, might be rendered irrelevant in the context of transreflectance. This is because when discussing transreflectance, one must consider the combined effects of both reflection and transmission. As such, the units utilised would be contingent upon the particular measurement technique and instrumentation employed.

During the experimental phase, when LA was diluted in ethanol to confirm the boundaries of intensity for signal acquisition and assess how the strong O-H bonds of ethanol could distort the spectra, the acquired signal proved to be notably weak. Consequently, due to time constraints, research efforts were redirected towards modifying the existing reactor design instead of fabricating a smaller volume reactor. The goal was to find a workaround, which involved the fabrication of a 'baffled-ring' designed to fit the existing reactor. The purpose of the 'baffled-ring' was to serve as a reflective surface positioned beneath the CaF_2 window, precisely where the beam is focused. The reflective surface was positioned as such to redirect the reflected beam back towards the interferometer, traversing a shorter path and preserving its intensity. The 'baffled-ring' was designed with specific criteria to ensure seamless integration with the existing reactor design, as outlined below:

- The baffles were strategically positioned to avoid obstructing either the inlets or the outlets of the reactor.
- The top surface of the ring was maintained at a distance of 200 μm from the CaF_2 window to facilitate robust IR signal acquisition back to the detector.
- Sufficient space was allocated within the design to accommodate the fitting of an impeller bar, ensuring efficient mixing during experimental procedures. The new reactor design featuring the reflective surface ('baffled-ring') is shown in Figure E-4.

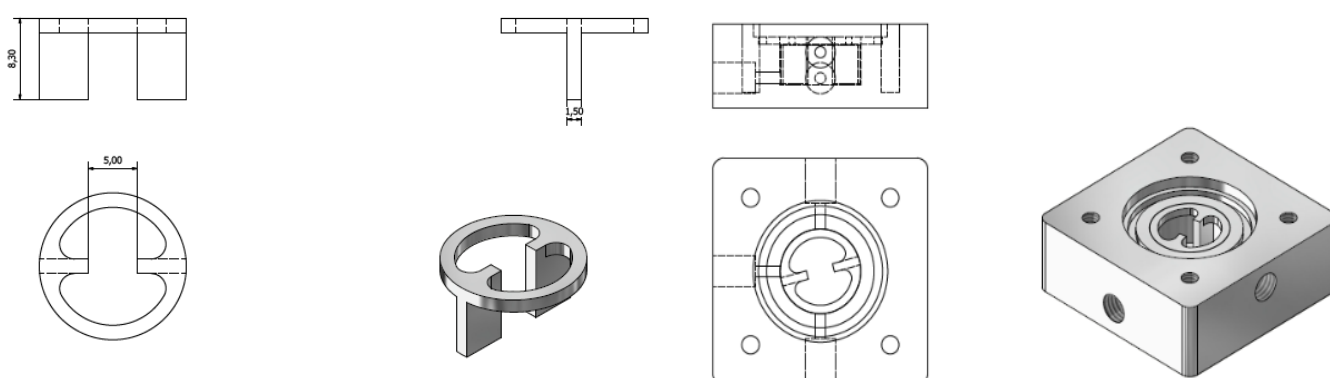


Figure E-4. CAD design of the reflective surface ('baffled-ring') and its integration into the m-CSTR.

Levulinic acid in ethanol in as low as 0.2M concentration was tested. In Figure E-5, the mapping of the area of the reflective surface is portrayed. As the FTIR microscope operated dually, the optical microscope first captured an image of the sample, and then IR analysis was

conducted at various spots within this image (denoted by cross-marks). The marks placed on the picture corresponded to the locations where IR spectra were obtained. Consequently, the colour of the IR spectra in Figure E-5 matches the marks on the image, allowing for easy correlation between the IR analysis and the specific spots within the sample captured by the optical microscope. Although, the main peaks of LA appeared inverted, the same spectrum can be obtained with varying intensities. The peaks correspond to the same wavelengths reported earlier for levulinic acid (Figure E-3), with the contribution of ethanol's O-H stretching peaks around 3300 cm^{-1} , C-H stretching vibrations around $2900\text{--}3000\text{ cm}^{-1}$ and C-O stretching peaks in the range of $1050\text{--}1150\text{ cm}^{-1}$.

Further investigation into the inverse appearance of the peaks was conducted by focusing the beam on the main body of the liquid, as shown in Figure E-6. The main body of the liquid is marked with the lilac cross-mark and the same colour IR spectrum. From Figure E-6, two key observations are made. Firstly, when directing the beam towards a reflective surface compared to the main liquid body, the interaction of light with the sample led to a reverse peak phenomenon, which may be solved by employing a common y-axis measure (reflectance) in the post-spectrum analysis. Secondly, although the spectrum obtained from the main body exhibits a lower SNR, the peak at 1700 cm^{-1} that belongs to the levulinic acid, remained visible. Post-processing the signal with baseline correction to offset the differences in intensities may yield fruitful results and a calibration methodology to quantify the concentration of the compound of interest, akin to the approach suggested by Moore et al. [493], can be pursued.

Despite consisting of raw data, these results demonstrated the feasibility of obtaining high signal intensity from relatively low concentrations of liquid-phase components within a reactor fitted with reflective surfaces, by employing an FTIR microscope. Further analysis on the hydrodynamics of this configuration is warranted to ensure that the reaction mixture concentration is evenly distributed throughout the reactor chamber, particularly in the space between the 'baffled-rings' and the CaF_2 window. Additionally, deeper investigation into how the light interacts with the liquid and the solid surfaces is of paramount importance. This exploration will enhance the interpretation of the spectral data obtained and contribute to the optimisation of the reactor design for coupling with FTIR micro-transflectance, thus expanding the applications of in situ IR spectroscopy in liquid samples beyond ATR.

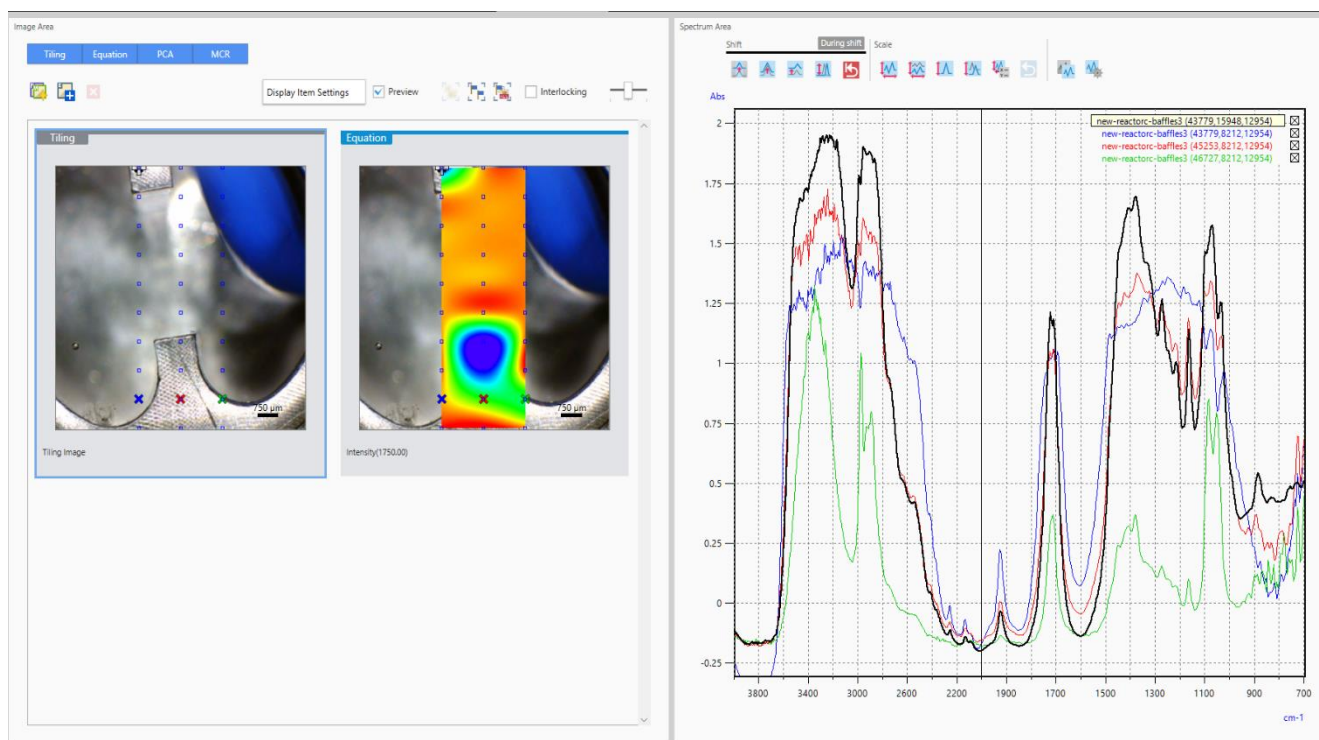


Figure E-5. Mapping of the reflective surface (picture on the left acquired with the optics lenses of the FTIR microscope) and the respective IR spectra (on the right) obtained from specific points on it, denoted by cross-marks, for a m-CSTR filled with LA 0.2 M in ethanol. The colours of IR spectra correspond to the colours of the cross-marks.

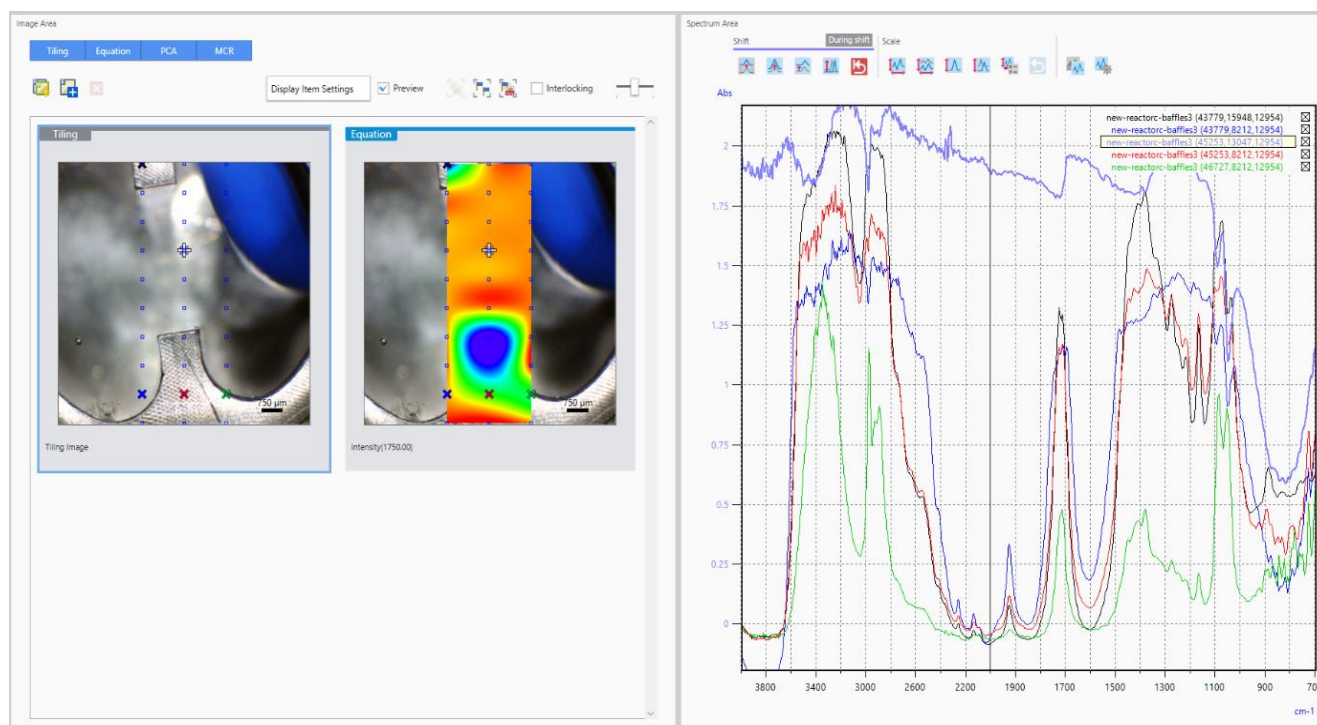


Figure E-6. Mapping of the reflective surface and bulk liquid (picture on the left acquired with the optics lenses of the FTIR microscope) and the respective IR spectra (on the right) obtained from specific points, denoted by cross-marks, for a m-CSTR filled with LA 0.2 M in ethanol. The colours of IR spectra correspond to the colours of the cross-marks. The IR spectrum in lilac was obtained from the bulk LA.

Appendix F. Activity coefficients and activities of feed and reaction mixture components for the esterification of levulinic acid to ethyl levulinate (SI from Chapter 7)

Table F-1. Activity coefficients, γ , and the corresponding activities, a , for the components of the esterification reaction feed for the different experimental conditions investigated in Chapter 4, calculated using Aspen Plus®, based on the UNIFAC thermodynamic model with Dortmund Data Bank parameters [470].

No	Temperature (°C)	Flowrate (μL/min)	$C_{LA,inlet}$ (M)	$C_{EtOH,inlet}$ (M)	$Y_{LA, inlet}$	$Y_{EtOH, inlet}$	$\alpha_{LA, inlet}$	$\alpha_{EtOH,inlet}$
1	70	20	0.8	15.723	1.577	1.003	1.262	19.837
2	70	20	1.6	14.320	1.417	1.012	2.266	32.456
3	70	60	0.8	15.723	1.577	1.003	1.262	19.837
4	70	60	1.6	14.320	1.417	1.012	2.266	32.456
5	100	20	0.8	15.723	1.099	1.001	0.879	13.819
6	100	20	1.6	14.320	1.071	1.003	1.714	24.550
7	100	60	0.8	15.723	1.099	1.001	0.879	13.819
8	100	60	1.6	14.320	1.071	1.003	1.714	24.550

Table F-2. Activity coefficients, γ , and the corresponding activities, a , for the components of the esterification reaction mixture at the outlet for the different experimental conditions investigated in Chapter 4, calculated using Aspen Plus®, based on the UNIFAC thermodynamic model with Dortmund Data Bank parameters [470].

No	Temperature (°C)	Flowrate (μL/min)	$C_{LA, outlet}$ (M)	$C_{EL, outlet}$ (M)	$C_{EtOH, outlet}$ (M)	$C_{W,outlet}$ (M)	$Y_{LA, outlet}$	$Y_{EtOH, outlet}$	$Y_{EL, outlet}$	$Y_{W, outlet}$	$\alpha_{LA, outlet}$	$\alpha_{EtOH, outlet}$	$\alpha_{EL, outlet}$	$\alpha_{W,outlet}$
1	70	20	0.389	0.415	15.316	0.415	1.552	1.004	1.946	2.480	0.603	15.380	0.808	1.030
2	70	20	0.894	0.704	13.620	0.704	1.389	1.014	1.734	2.406	1.243	13.813	1.221	1.694
3	70	60	0.610	0.187	15.537	0.187	1.566	1.004	1.969	2.487	0.955	15.592	0.368	0.465
4	70	60	1.302	0.319	14.027	0.319	1.400	1.013	1.780	2.401	1.823	14.211	0.568	0.766
5	100	20	0.073	0.728	15.001	0.728	1.069	1.003	1.577	2.407	0.078	15.044	1.149	1.753
6	100	20	0.229	1.350	12.954	1.350	1.035	1.009	1.479	2.371	0.237	13.070	1.997	3.202
7	100	60	0.311	0.475	15.239	0.475	1.079	1.002	1.598	2.420	0.336	15.269	0.759	1.150
8	100	60	0.701	0.883	13.427	0.883	1.046	1.006	1.506	2.388	0.733	13.514	1.330	2.110