Book of abstracts

Maxime BODDAERT et al.	A miniaturized ozonolysis flow platform for expeditious sulfur mustard warfare simulant neutralization
Aravind Senthil VEL et al.	Enhancing (Mixed-Variable) Reaction Optimization in Autonomous Flow Reactors through Filtering-Assisted Optimization
Leyla ALIYEVA et al.	Synthesis of Hydroxyapatite Nanoparticles in Microfluidic System with Different Capillary Arrangements
Joseph FARAH et al.	Nanohybrids in microfluidic chips for hydrogen production and catalysis
Elias ABEDELNOUR et al.	Functionalization of organic molecules in a gas/liquid plasma microreactor without metal catalysts
Claudio LEHMANN et al.	Autonomous online optimization in flash chemistry using online MS
Catherine GOMEZ et al.	Eco-friendly Syntheses of Metallic Bismuth Nanoparticles _Scale-up on semi-pilot reactors
Léna BRASSART et al.	Flow technology-enabled direct chloromethylation of esters
Vugar KHALILOV et al.	Development of a Microfluidic Process for the Production of Polyelectrolyte Complex Nanoparticles
Francisco BOLAÑOS GARCIA et al.	Effects of transient behaviour in slug flow chemistry platforms
Ryma BENRABAH et al.	Development of a microfluidic reactor for testing jet-fuel oxidation stability and its use with a SAF surrogate

A miniaturized ozonolysis flow platform for expeditious sulfur mustard warfare simulant neutralization

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Résumé

Chemical warfare agents (CWAs) are extremely toxic synthetic molecules for mammals. Among them mustard gas or yperite (**HD**) has one the most significance in military terms. **HD** as a sulfur mustard is labeled as blister agent or vesicant and used for incapacitation. Causing severe eye injuries, respiratory irritation and skin burn and painful blistering. Standard methods of decontamination rely on either hydrolysis or chemical oxidation with aqueous bleach. Despite their effectiveness, these methods generate a fair amount of aqueous wastes that needs to be retreated at dedicated facilities. Herein is presented a study aiming at chemical neutralization of **HD** in organic medium using ozone. All the work was conducted with HD simulants named 2-chloroethyl ethyl sulfide (**CEES**) and 2-chloroethyl phenyl sulfide (**CEPS**) to develop a method of mustard neutralization using continuous flow technology that would drastically reduce the amount of toxic aqueous wastes produced. The optimization of the reaction conditions led to a full conversion both **CEES** and **CEPS** with a high selectivity toward their non-toxic sulfoxide counterparts after 1 s of reaction time at 10 ∘C.

Enhancing (Mixed-Variable) Reaction Optimization in Autonomous Flow Reactors through Filtering-Assisted Optimization

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The digital revolution in chemistry has transformed the approach to chemical reactions, resulting in significant time savings and increased efficiency. Integration of autonomous flow reactors, combining flow chemistry, inline monitoring tools, and computer control, streamlines the process of conducting and analyzing reactions for more efficient optimization strategies.
Traditionally, chemists relied on trial-and-error methods for parameter optimization. However, the use of algorithms in autonomous flow reactors has enabled improved reaction optimization, saving time and resources. While existing optimization methods handle continuous variables, the popular High Throughput Screening (HTS) method addresses discrete variables. However, HTS - Brute Force method - has limitations, such as expert interpretation requirements and neglect of continuous variable effects.

To overcome these limitations, we developed the Sampling Filtering Optimization (SFO) approach as an alternative to HTS. SFO involves analyzing samples from different conditions using analysis of variance (ANOVA) to identify optimal catalysts and solvents (1). By employing SFO, we achieve efficient optimization of reactions with discrete variables.

Recently, Bayesian optimization has gained popularity for handling discrete variables, but its potential as an HTS replacement remains uncertain. Previous research focused on limited discrete combinations, leaving questions about its performance with a larger set of variables.

This study explores the potential of Bayesian optimization by applying filtering and conducting optimization with potential catalysts.

Experimental investigations compared three approaches: SFO, classical Bayesian optimization, and Bayesian optimization with filtered potential catalysts (2). Results demonstrate significant performance improvement in Filtering-assisted Bayesian optimization compared to classical Bayesian optimization.

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2 A. S. Vel, K. E. Konan, D. Cortés-Borda and F.-X. Felpin, Org. Process Res. Dev., 2023, DOI:10.1021/acs.oprd.3c00238.

Synthesis of Hydroxyapatite Nanoparticles in Microfluidic System with Different Capillary Arrangements

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Hydroxyapatite (HA; $Ca_{10}(PO_4)_6(OH)_2$) is widely used in tissue engineering, bone and teeth repairs due to its biocompatible, biodegradable properties and analogy to natural bone.[1] HA is known as a good bone graft materials with its high bioactivity offering a robust chemical bond with the native bone tissue. HA can be obtained from natural origins or by different synthesis methods. Generally, wet-chemical precipitation[2], solid-state reactions[3], sol-gel chemistry[4] ways are mainly applied to synthesize HA nanoparticles. Sol-gel approach is more advantageous due to its simplicity, versatility, homogeneity in product, purity and low synthesis temperature, etc.[5] This communication will report for the first time the use of a capillary-based microfluidic device[6] to produce HA nanoparticles with enhanced properties compared to the widely reported batch approach (Figure 1). For this purpose, different capillary arrangements (core-shell variations, side-by-side) were studied. The obtained nanoparticles were investigated by different characterization methods and comparatively studied with characteristics of HA nanoparticles obtained from the conventional sol-gel method. The particle size, morphology, chemical structure, phase analysis and specific surface area were analyzed by scanning and transmission electron microscopy, X-ray diffraction, Fourier transform infrared spectroscopy, and Brunauer-Emmett-Teller experiments.

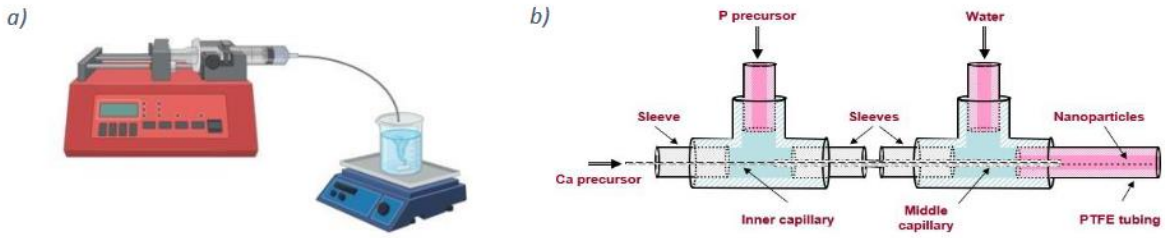

Figure 1. Approaches used for the synthesis of HA nanoparticles: a) batch and b) microfluidic.

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Nanohybrids in microfluidic chips for hydrogen production and catalysis

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In recent years, microfluidics has shown great promise in the field of photocatalysis and heterogeneous catalysis. Microfluidic reactors allow fine control of energy and material transfers under optimal safety conditions. However, the development of functional and easy-to-implement strategies for combining microfluidics and nanocatalysis remains necessary. From this perspective, this work aims at developing not only microfluidic chips as microreactors but also hybrid catalysts supported on carbon nanotubes (CNT) and their integration on chips. Three fields of application have been considered: i) heterogeneous catalysis, ii) photocatalyzed production of hydrogen, and iii) photocatalytic degradation of toxic compounds (figure 1).

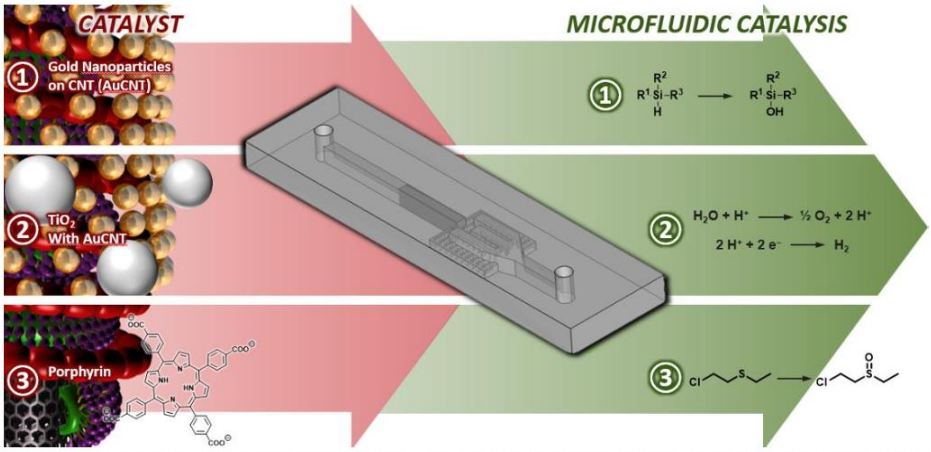

Figure 1: Nanohybrids supported on carbon nanotubes for hydrogen production and catalysis in microfluidics.

In the first part, the aerobic oxidation of silanes to silanols was studied to evaluate the advantages of microfluidics compared to the same reaction conducted in a traditional batch reactor.1 Hybrid catalysts, made of gold nanoparticles on carbon nanotubes (AuCNT), are created using a layer-by-layer method. The carbon nanotube support's morphology makes it ideal for integration into microreactors, ensuring efficient and reusable catalytic systems for sustainable chemistry. In the second part, the production of hydrogen was demonstrated by photocatalyzed dissociation of water using titanium dioxide nanoparticles (photocatalysts) associated with AuCNT (co-catalysts). A device adapted to the continuous production of hydrogen has been developed.2 In the last part, a microfluidic process was studied for the catalytic degradation of a mustard gas simulant. This process involved a continuous flow photochemical reaction catalyzed by a porphyrin.

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Développement de la synthèse et de la fonctionnalisation d'amines assistées par plasma dans un microréacteur à flux gaz/liquide.

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La recherche de nouveaux outils et méthodologies pour une synthèse chimique plus verte et durable demeure une priorité. Ce travail présente l'utilisation d'un microréacteur à flux gaz/liquide pour la synthèse assistée par plasma gazeux. [1,2] Le plasma gazeux, riche en espèces réactives telles que les électrons, les radicaux et les ions, offre une alternative prometteuse aux catalyseurs métalliques et aux additifs. Diverses N-acylamines ont été synthétisées en exposant une solution d'amine primaire ou secondaire dans un ester à un plasma d'argon, obtenant ainsi des amides avec de bons rendements. [3] Par ailleurs, en utilisant le réactif de Ruppert-Prakash (TMSCF [3]) comme donneur de groupe fonctionnel, les amines ont été fonctionnalisées. Le traitement d'une solution d'amine dans le TMSCF [3] par un plasma d'argon a conduit à la formation de trifluoro N,N-aminales avec de bons rendements, ces aminales constituant des précurseurs intéressants et étant converties en trifluoroéthylamine.[4] La généralisation des deux procédés a été explorée, les limites ont été identifiées, et des études mécanistiques ont été réalisées, aboutissant à la proposition de mécanismes réactionnels.

Pour aller au-delà de ces résultats, il serait intéressant d'explorer l'utilisation d'autres solvants dans ce procédé, afin de déterminer leur impact sur les rendements et la sélectivité des réactions. De plus, l'optimisation et l'échelle de ces synthèses dans un contexte industriel doivent être envisagées pour évaluer leur viabilité à grande échelle. Ces investigations pourraient ouvrir de nouvelles perspectives pour une chimie plus durable et des applications industrielles plus larges.

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Autonomous online optimization in flash chemistry using online MS

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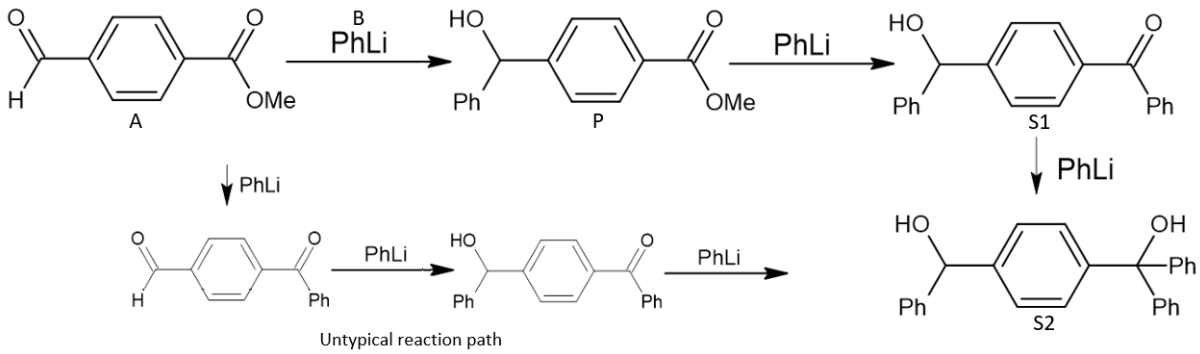
Autonomous online optimization facilitates the optimization of a reaction during process development. Complete automation of this procedure, without the need of human intervention, drastically reduces the time and effort required. We developed a platform for autonomous online optimization using quantitative online mass spectrometry (which is rarely used as process analytical technology) and two different optimization algorithms (Bayesian optimization and SNOBFIT[1]) for comparison, and demonstrated its applicability in real case applications using an example of flash chemistry: the mixing sensitive reaction of Methyl-4-formylbenzoate with Phenyllithium. [2]



Scheme 1: Reaction scheme of the reaction of Methyl-4-formylbenzoate (A) with Phenyllithium (B)

Automated response factor fitting has been used to obtain quantitative data from mass spectrometry. Assuming that all species can be observed, that there are no unknown side reactions occur (i.e. a closed mass balance) and that there is a linear correlation between MS signal and the concentration, a linear system of equations can be set up and solved by varying the response factors. In this way, quantitative data can be obtained without the need for calibration like shown in Figure 1.

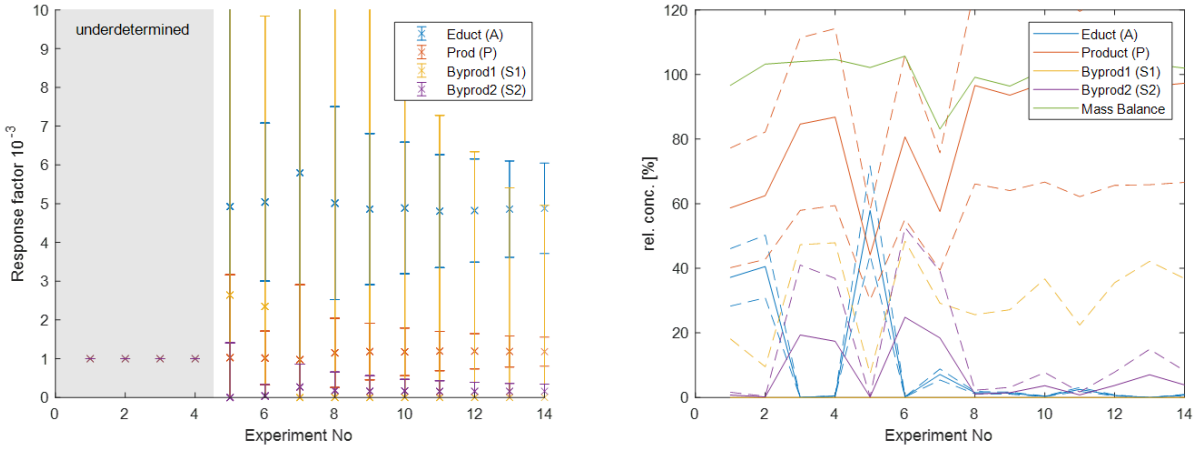


Figure 1: Left: Progress of the fitted response factors during an optimization run. Right: Concentration curves over the optimization run, calculated with the final response factors. Confidence intervals: 95 %.

MS data is used for online optimization. Figure 2 shows an example of the final objective function model and the progress of the optimization using the product peak area as the objective for Bayesian optimization. This approach allows the process to be optimized quickly and reliably, as demonstrated by a comparison of multiple experiments. Quantitative data also allows other objectives to be considered, such as product concentration or undesired byproducts. Finally, a comparison proves the advantage of the more recently considered Bayesian optimization over the earlier established SNOBFIT algorithm.

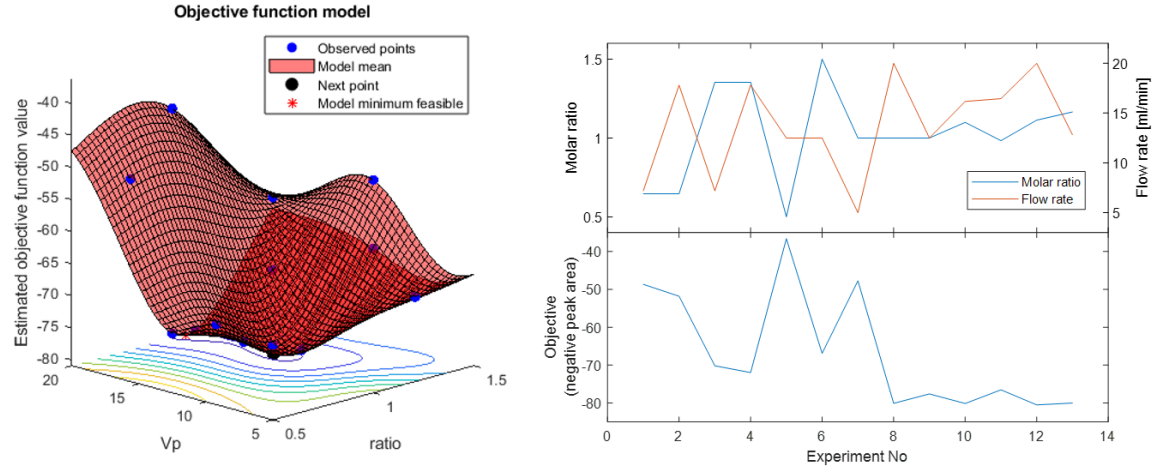


Figure 2: Left: Bayesian optimization objective function model of the product peak area as objective. Right: Progress of the optimized parameters and the objective during the experiments.[3]

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Eco-friendly Syntheses of Metallic Bismuth Nanoparticles Scale-up on semi-pilot reactors

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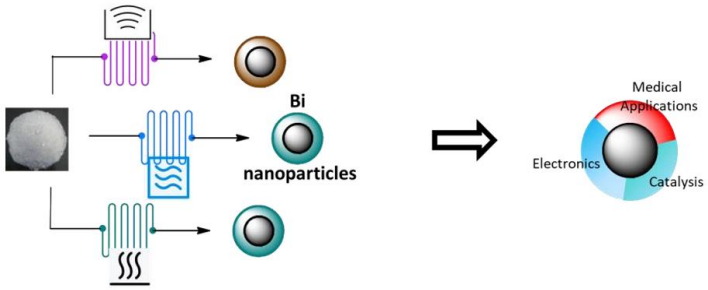
The attractiveness of nanoparticles has changed considerably over the last few decades, making it necessary to develop new synthesis routes.[1] Despite their sometimes controversial use, the interest in nanoparticles is justified by their many properties (surface atoms, high surface energy, small size). As a result, their field of application is very broad, covering the fields of optics, catalysis and medicine.[2] However, this strong development is often thwarted by the use of synthesis methods that are not very economical, generate a lot of waste and use toxic reagents or non-green solvents. Traditionally, metallic nanoparticles have been synthesized in batch following a bottom-up approach using thermal decomposition, polyol processes or salt reduction.[3] These methods have also revealed the constraints of nanoobject instability, poor control of their polydispersity and a lack of reproducibility. It has therefore proved necessary to propose new strategies. Our aim has been to develop more efficient synthesis devices in terms of efficiency, productivity and also safety when using more stringent reaction conditions. In this context, an opening was made by developing new syntheses of metallic bismuth nanoparticles in continuous flow. Our study focused on the use of greener conditions in the choice of reagents and solvents. In order to also optimise energy costs, continuous flow was coupled with different activation methods such as microwave irradiation,4 sonication5 and thermal energy. A scale-up was also considered and compared between home-made and commercial reactors in order to study its impact on nanoobjects.



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Flow technology-enabled direct chloromethylation of esters

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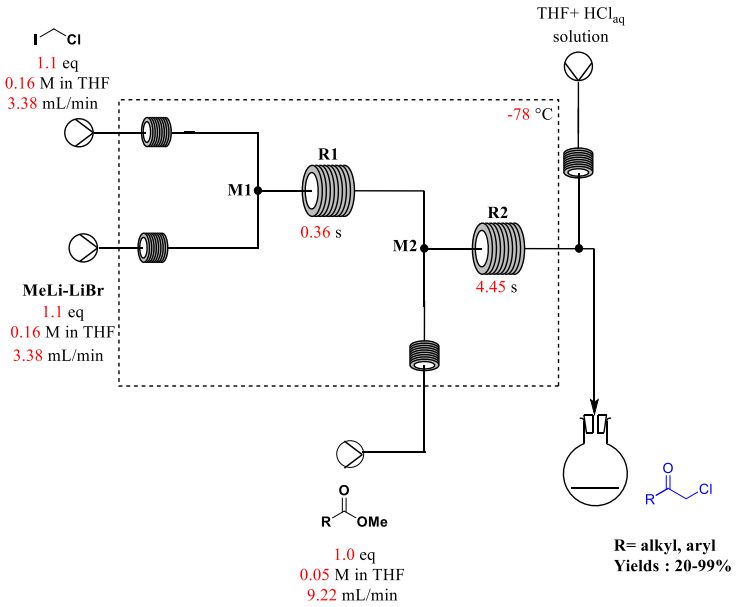
Continuous flow chemistry has offered since several decades a lot of benefits concerning reaction efficiency, safety, scalability, selectivity and temperature control. It is particularly appealing for processes implying highly reactive organometallic intermediates, as demonstrated by Yoshida and others.[1] Flash chemistry, which combines flow microreactor technology and very short residence time, allows efficient and selective carbon-carbon or carbon-heteroatom bonds formation.[2] Therefore, arduous processes or even impossible chemistry with conventional batch reactors, such as external trapping of reactive carbenoids with electrophiles, can be achieved.[3]

Flow chloromethylation has shown to be an attractive way to access chloromethylketones, which are valuable synthons that can be post-functionalized for bioactive compounds preparation.[4] In this work, we developed a new procedure by taking advantages of flow chemistry to trap thermally unstable chloromethyllithium intermediate with esters, challenging electrophiles, due to a limited relative reactivity. Thus, thanks to precise control of the residence time and of the stoichiometry, the chloromethylketone products can be chemoselectively obtained with high optimized yields. This novel method has been applied on a large range of functionalized esters with good to excellent yields.



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Development of a Microfluidic Process for the Production of Polyelectrolyte Complex Nanoparticles

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This study delves into the production of polyelectrolyte complex nanoparticles (PEC NPs) via microfluidics, aiming to optimize experimental conditions and address challenges for enhanced nanoparticle size control and reproducibility. Preliminary batch experiments systematically explore the influence of electrostatics and precipitation phenomena, revealing the formation of PEC NPs with notable polydispersity. Systematic optimization of operating conditions, *i.e*. continuous and dispersed phases flow rates or PEC concentration etc., is meticulously conducted to improve PEC NP production efficiency. Various modifications to the experimental setup, such as adjusting system inclination and substituting collection vessels, are implemented to mitigate challenges like accumulation in the collecting tube and capillary clogging. These modifications result in improved control over PEC NP size and size distribution. Despite persistent challenges, the stability and reproducibility of PEC NP production are diligently maintained. Future research directions encompass exploring alternative size control methods and further optimizing system design.

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Effects of transient behaviour in slug flow chemistry platforms

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In recent years, there has been a notable emergence of various flow chemistry platforms designed to automate experimentation of chemical synthesis processes, optimize reaction conditions [1-3], and in some instances, even propose kinetic models [3]. Many of these platforms operate in steady-state configuration with a continuous flow due to its simplicity. However, some slug flow methodologies have been reported [3], where discrete slugs of reagents are injected. This approach minimizes the required amount of reactive material, thereby reducing experimental costs and enabling the execution of a greater number of experiments.

To mitigate the effects of dispersion [4], gas injection between slugs is employed. Nevertheless, the automation with gas-liquid segments poses technical and expertise-related challenges. Consequently, it is interesting to explore whether a slug flow configuration, despite dispersion effects, can provide valuable data for determining kinetic parameters.

In order to achieve this, a one-dimensional model was build using a set of partial differential equations (PDEs) to depict the injection of discretized volumes of reactive material. The model was solved utilizing a finite volume solver, FiPy [5], implemented in Python, to determine the conversion at the end of the reactor. Analysis of the results revealed the impact of varying the volume of reactive slugs. Notably, reducing the slug volume led to a greater difference between the observed conversion and the conversion expected under steady-state conditions, indicative of the potential to evaluate fast kinetics.

However, it's important to note that the simulation process demands several minutes to conclude, which makes it unfeasible for optimization algorithms requiring numerous iterations. An artificial neural network (ANN) was constructed in order to get around this restriction, resulting in a significant reduction in simulation time. Kinetic parameters can be determined by minimizing the mean squared error (MSE) between the conversion predicted by the trained model and the experimentally observed conversion. This approach enables the use of transient-state slug flow platforms to be used for kinetic parameter estimation.

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Development of a microfluidic reactor for testing jet-fuel oxidation stability and its use with a SAF surrogate

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One potential solution to diminish the aviation carbon footprint is to blend Sustainable Aviation Fuel (SAF) into jet fuels. However, the thermal stability and oxidation stability of standard jet-fuels may be affected by the addition of SAF [1]. In this work, we developed a Si-glass microfluidic reactor with a fluid supply made of inert polyether ether ketone (PEEK). The experimental rig PEEK-ACHU (Autoxidation µChip Heated Unit) was used to investigate the oxidation stability of a SAF surrogate. A mixture of n-decane and iso-octane was used as the surrogate SAF [2]. The thermal oxidation stability of the mixtures was measured in the microreactor, working at conditions up to 453 K and 30 bar, with a gas-liquid segmented flow that allows the liquid oxidation to occur in homogeneous, self-agitated liquid slugs. PEEK-ACHU allows residence times as long as 2 hours to be reached on a 4-inch diameter silicon chip, visual access to the reactor, and a well-defined kinetic study of the liquid fuel autoxidation. The total hydroperoxide concentration was quantified at the exit of the microreactor using a specifically designed HPLC device with a post-column reactor [3]. The results of this study show that the microfluidic apparatus is able to perform reliable autoxidation measurements and allows a better understanding of the kinetics. The self-agitation allows a homogenous phase, and the visual access of the reactor is relevant for other applications, such as spectroscopic monitoring of deposit formation.

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