Combining Automated Microfluidic Experimentation with Machine Learning for Efficient Polymerization Design

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Understanding polymerization reactions has challenges relating to the complexity of the systems, hazards associated with the reagents, environmental footprint of the operations, and the highly non-linear topologies of reaction spaces. In this work, we aim to present a new methodology for studying such complex reactions using machine-learning-assisted automated microchemical reactors. A custom-designed rapidly prototyped microreactor is used in conjunction with in situ infrared thermography and efficient, high-speed experimentation to map the reaction space for a zirconocene polymerization catalyst. Chemical waste was decreased by two orders of magnitude and catalytic discovery was performed in one hour. Here we show that efficient microfluidic technology can be coupled with machine learning algorithms to obtain high-fidelity datasets on a complex chemical reaction.

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Abstract
Understanding polymerization reactions has challenges relating to the complexity of the systems, hazards associated with the reagents, environmental footprint of the operations, and the highly non-linear topologies of reaction spaces. In this work, we aim to present a new methodology for studying such complex reactions using machine-learning-assisted automated microchemical reactors. A custom-designed rapidly prototyped microreactor is used in conjunction with in situ infrared thermography and efficient, high-speed experimentation to map the reaction space for a zirconocene polymerization catalyst. Chemical waste was decreased by two orders of magnitude and catalytic discovery was performed in one hour. Here we show that efficient microfluidic technology can be coupled with machine learning algorithms to obtain high-fidelity datasets on a complex chemical reaction.

Main
The advent of synthetic plastics over the last century has drastically reshaped the chemical industry and the world at large. Long-chain α-olefin polymers are most often synthesized using specialized catalysts that are carefully selected both for end-product performance and optimal process economics \(^1-^3\). The discovery and design of conditions related to these catalysts is a time consuming, wasteful, and expensive process. Single site catalyst research alone is estimated to have spent 5 billion dollars by the year 2000, with the entire polymer industry being worth $611.9 billion in 2017 \(^4,^5\). Traditional batch-based catalyst discovery consumes liters of solvent per trial and results in large quantities of chemical waste. Additionally, catalysts and the associated activators are expensive and may be hazardous, exemplified by the commonly used activator...
trimethylaluminum \(^6\). Homogenous catalytic polymerizations are an active area of research due to advantages in control of the polymer product as well as environmental benefits in the manufacturing process \(^2,7\). However, problems with dissolved homogeneous catalyst recovery and recycling arise due to difficulty in separation from the solvent under mild conditions that would preserve catalyst activity. Major aims are to reduce the amount of catalyst, activator, and solvent used per experimental trial along with minimizing the actual number of trials needed to complete a study.

The current state of polymer manufacturing has an environmental impact as a vast amount of energy is used to convert petrochemicals into commodity plastics including poly(ethylene) and poly(propylene). It is estimated by the U.S. Department of Energy that about 6% of all energy produced in the United States is used in the production of polymers \(^8\). More importantly, about 37% of all global greenhouse gasses (GHG) are created directly or indirectly by polymer manufacturing \(^9\). In an industry that has shaped the world as we know it and is continuing to expand rapidly, innovative solutions are needed to quickly engineer and understand new production pathways \(^10\). Design of laboratory-scale reactors for quick discovery and integration of machine learning for robust process understanding are two possible ways to work towards developing more efficient polymerization catalysts while minimizing environmental harm. Efficient and automated experimentation could reduce experimental times from months to minutes and reduce chemical waste by several orders of magnitude.

Zirconocene-based alkene polymerization catalysts were derived from the knowledge gained on titanium-based metallocene catalysts originating from the works of Ziegler and Natta \(^11\) with significant early advances made by Chein \(^12\), Kaminsky \(^13\), Brintzinger \(^1\) and Rieger \(^14\). Additional important studies were carried out since then by various groups investigating both the catalysts and resultant polymers using numerous techniques \(^15–17\). Many novel methods have been applied to the study of these catalysts including Quantitative Structure Activity Relationship (QSAR) \(^18\), Mass Spectroscopy (MS) \(^19,20\), cyclic voltammetry \(^21\), and Nuclear Magnetic Resonance (NMR) \(^22–26\). However, many of these laboratory techniques are inherently limited by throughput as they rely on batch experimentation, relatively large quantities of reagents, and bulky spectroscopic equipment, greatly limiting the time-to-market of promising new catalyst compounds. Additionally, designing zirconocene catalytic reactions is a challenge, as the ratios of reagents, activator composition and temperature play
competing roles. A method in which large amounts of potential candidate molecules can be screened, using \textit{in-situ} thermography to quantify catalytic activity based on a reactor volume’s exotherm, has not yet been developed.

Microreaction engineering has evolved in the last few decades due to the benefits it offers for controlling chemical reactions. Decreasing the volume of the reactor enables careful manipulation of heat and mass transport physics for desired performance. Additionally, microreactors allow for the integration of novel non-interfering \textit{in-situ} and \textit{in-operando} spectroscopic methods. Microfluidics have been applied to numerous kinetics and first principles research problems including applications in pharmaceuticals, fine chemicals, and petrochemicals. These recent developments were driven by a desire to perform experiments more quickly, maintain better control over the reaction environment, and reduce waste in chemical research. There have been a number of studies in recent years integrating spectroscopic techniques. Overall, the rapid understanding and reaction design of metallocene catalysts has potentially large implications on the environmental footprint of polymer manufacturing. This acceleration in designing catalytic reactions can be accomplished using spectroscopic microreactors with machine intelligence.
A recently discovered catalyst of interest to academia and industry is (SBI)ZrMe₂ (I) in conjunction with a B(C₆F₅)₃ (II) activator. This combination is active with a broad range of α-olefins, creates polymers with desirable properties, and reduces the reliance on dangerous activators like trimethylaluminum. Recently there have been several papers published about this and related catalyst systems aimed at understanding the kinetics and design of the reactions with a general reaction mechanism seen in Figure 1. Our findings expand upon these seminal works through a semi-automated study of the catalyst’s behavior to quickly estimate the reaction space topology. Herein traditional data analysis and visualization is supplemented using the Artificial Neural Networks (ANNs) as a nonlinear fitting tool to model and predict catalytic behavior without knowledge of the model’s underlying dependencies and degrees.

This work seeks to address two main challenges, one being the design of flow-based microsystems for the quick and efficient screening of catalyst for exothermic chemical processes and the second being extracting the most information possible out of a given set of experiments. The first challenge is addressed through the creation of an integrated continuous flow microfluidic platform which incorporates pumps, manifolds, controls,
and analytics into a singular interface which is amenable to automation and integration with analytical
techniques. Due to heat and mass transport considerations, flow-based microreactors are challenging to use for
such polymerization reactions, necessitating careful design and selection of operating conditions to ensure high
data fidelity with minimal transport limitations and safe operation with dangerous chemistries. The second
challenge is addressed through the use of rational experimental design to sample an entire experimental space
quickly and efficiently while extracting information of interest from a non-invasive and real-time thermal
camera. Neural networks were used as a fitting tool to supplement the analysis by modeling and visualizing the
behavior of the experimental space. Overall the system and process presented address current trends intersecting
chemical engineering and computer science by integrating microscale reactions with automated experimentation
and ML-enhanced process understanding.
Microreactor Design

Microfluidic platforms are uniquely suited for the study of olefin polymerizations as these exothermic reactions take place very quickly, have multiple reaction pathways, require precise control, generate large amounts of chemical waste, and use expensive and difficult to synthesize catalysts. Microfluidics have already been successfully applied to the research of various polymerizations and other exothermic reactions \(^{41-44}\).

The first step in our design of an intelligent microsystem is an order-of-magnitude estimation of heat and mass transport properties and dimensionless numbers including the Damköhler number (defined as the reaction rate: mass transport rate, \(Da = kC_0^{n-1} \tau\), where \(k\) is the reaction rate constant, \(C_0\) is the initial concentration, \(n\) is the reaction order and \(\tau\) is the residence time; Beta number (heat generated: heat removed, \(\beta = -(r\Delta H_{rxn}d_F^2)/(4\Delta T_{ad}\kappa)\)), where \(r\) is the reaction rate, \(\Delta H_{rxn}\) is the heat of reaction, \(d_F\) is the diameter of the channel, \(\Delta T_{ad}\) is the adiabatic temperature change, and \(\kappa\) is the thermal conductivity; and the Reynolds number (inertial forces: viscous forces, \(Re = \rho VL/\mu\)), where \(\rho\) is the density of the fluid, \(V\) is the velocity, \(L\) is the characteristic length, and \(\mu\) is the viscosity. Knowledge of these quantities enables the design of microfluidic devices which offer scalable chemical data mimicking the physics found in industrial-scale processes and enabling visualization. Additionally, this provides context for analyzing other properties of interest such as stream mixing, dispersion, heat transfer, mass transfer, and the reaction kinetics. Here the microreactor was designed such that the Damköhler number can be varied between 0.3-101, enabling the sampling of both reaction rate limited and mass transport limited regimes. The Beta number varies between \(O(10^{-3})\) and \(O(10)\) based on standard heat of polymerization of 1-hexene (III), indicating that more heat is generated than removed, enabling thermographic analysis \(^{45,46}\). Finally Reynolds number is variable between \(O(10^{-3})\) and \(O(1)\), meaning that the reaction is operating in a laminar flow regime. The final design for the reactor can be seen in Figure 2a. Overall the analysis and understanding of heat and mass transport characteristics is important to the efficient functioning of the reactor and accurate data collection.
Figure 2: (a) CAD rendering of assembled reactor with thermal management and fluid delivery systems. The different components seen include the reactor, compression O-rings, fluid interface connections, Peltier cells for heating/cooling and a liquid cooling block to ensure stable thermal performance; (b) Finite Element Analysis (FEA) simulation of the reactor surface measuring the infrared irradiance (W/m²) with a 20 K temperature gradient between the fluid and reactor; (c) Image of the reactor channel with no flow; (d) Image of the reactor with a fully developed reactive flow.

System characterization

Next, the design of an intelligent microreactor involves the characterization of desired operation, both computationally using Finite Element Analysis (FEA) and analytically with methods such as Residence Time Distribution (RTD) studies with chemical tracers. These analyses help with fully characterizing the system and calibrating the analytical methods. FEA simulations were carried out, verifying a perceptible difference in infrared radiative flux between a warm reactor channel and the ambient reactor. The results of this simulation can be seen in Figure 2b, showing a roughly 30 W/m² difference in flux with a 20 K temperature gradient. Experiments were then carried out to verify the thermal performance of the microreactor. Reagent concentrations from previous literature were injected into the reactor and the exotherm was observed. Figure
2c-d show thermographic images of the reactor, highlighting the development of reactive flow as the reagents mix. The catalyst flows through the far feed channel, and the activator flows through the closer one. Upon contact a change in radiation is observed, as indicated by the lighter blue color. It is further observed that the reaction is initiated almost instantaneously when the reagents mix, with the strongest thermal signature in the first centimeter of the channel.

Finally, the microsystem design involves its integration with analytical methods including both in and ex-situ measurement techniques. Accurate and precise control along with a diversity of measurable variables are critical to creating an accurate digital twin computer model of the complex polymerization. A challenge presented by a flow-based testing platform is the inclusion of calibrated pumps and manifolds not present in a traditional batch system. Other critical considerations are temperature mapping and homogeneity, which are uniquely difficult for in typical flow reactors but are made simpler using microsystems. The successful analysis, testing and integration of all these aspects results in a system which provides relevant data quickly and accurately, with an overview of the experimental system being summarized in Figure 3. Overall analysis and implementation of microsystems has emerged in pharmaceuticals and fine chemicals through robust understanding and reaction design.\textsuperscript{47,48}
Algorithmic concept

The current work seeks to develop a methodology for the testing, design and general understanding of one class of zirconocene-based catalyst by using a ANN fitting. The algorithm, used as a form of supervised Machine Learning (ML), aids in our understanding of the complex kinetics and reaction design for a homogeneous catalyzed polymerization. Fitting of traditional numerical models involves understanding the degree of dependence of various independent variables (I.e. linear, polynomial, natural exponential, etc.), thus an ANN is demonstrated as a potential way to construct a functional model without a rigorous understanding of
the underlying mechanism. Recently we demonstrated that ANNs can be used as a tool for modeling and understanding complex catalytic pathways for polymerization reactions from a first-principles \textit{in silico} approach \cite{49}. A Design of Experiments (DoE) strategy employing fractional factorial design is used to maximize the data collected while minimizing the number of experiments performed (Monte Carlo and quasi Monte Carlo techniques can be used with sampling algorithms including Latin Hypercubes and Sobol sequences may also be used for greater sensitivity analysis \cite{50}). The integration of these steps together compounds the energy, cost, and, environmental impact savings of using a smaller lab space, with fewer trials, in a fraction of the time and labor. This enables faster data collection and development of models while reducing the time and amount of chemical waste generated. This methodology serves as a proof-of-concept for using DoE algorithms with ANN fitting and spectroscopic microfluidics to quickly gain process understanding.

The concept presented herein is that a semi-autonomous reaction system can perform as a machine-assisted chemist to understand the complex reaction space for a homogeneous metallocene catalyst. The first component of this is control and data interpretation systems which perform the experiments, gather the data and generate the fitted ANN models. An overview of the system used can be seen in the top panel of Figure 4. The process was controlled by a combination of MATLAB and LabVIEW as both components offer certain advantages. MATLAB allows for the development of advanced computational algorithms and includes a robust machine learning toolbox with different training algorithms. LabVIEW offers a real-time control environment with independent loops running to provide control of the system, including interfacing with external devices. Reagent mixing was provided by electromagnetic diaphragm pumps; flow through the reactor was established by use of a pressure controller and thermal control was established through Peltier elements. A full description of the system can be found in the methods section, page 3, of the supporting information.

Data collected from the infrared camera was segmented into feed, reaction, and background zones to enable further calculations. Reaction exotherm data was used to interpret the catalytic productivity, mainly the grams of polymer produced per (mole catalyst • mole monomer • hour). Catalytic productivity is an important metric for polymerization catalyst design and is used when discovering new catalysts, understanding existing catalysts, and designing industrial plants. Due to the environmental concerns associated with catalyst production and
reagent recycling including greenhouse gas emissions and chemical waste, it is important to adjust catalytic performance to meet optimistic goals and government regulations. By interpolating the data from a minimal number of experiments using a quick and efficient fitting algorithm, it becomes possible to visualize the full range of the experimental topology which could not be achieved using traditional trials.
Automated experimentation

Experimentation was conducted in such a way as to establish an understanding of the reaction space without the need for extensive trials. First the reagents were manually prepared in an inert environment glovebox and connected to the experimental manifolds. From there an automated routine was used to establish control, clean the reactor, and perform experiments, with a flowchart presented in the bottom panel of Figure 4. The purpose of the algorithm was to efficiently perform experiments in an automated fashion. The next experimental point is selected from a specified monomer, catalyst, activator concentration bank based on the recommendation of a DoE algorithm. Automated experimentation allows for efficient experimental management, real-time reaction monitoring, active feedback, and integrated control while providing training data for the ANN to analyze. The experimental system consisted of the reagent mixing and storage equipment, thermal control, the reactor, and associated control systems with Figure 3 showing an experimental flowchart. The reactor and thermal camera were contained within a vacuum enclosure to reduce the effect of atmospheric interference. The reactor used in this study was fabricated by photopolymerization stereolithography and bonded to an infrared transparent fluoropolymer film, with an overview of the reactor assembly and dimensions seen in Figure 2a. More information about the construction and integration of the reactor and various systems can be found in the supporting information.

Overall the process and system were designed to meet several design challenges. The chosen catalyst and activator molecules are highly sensitive to moisture and oxygen, and must therefore be handled in such a way that they never come into contact with the atmosphere. Additionally, the solvent and monomer used present safety concerns as they are both toxic and highly flammable, producing vapors that may be explosive. The next challenge in the system design was the integration of robust process automation. The experiment needed to integrate a thermal camera, analytics and fluid handling seamlessly and autonomously. This was accomplished
through the use of different software packages and the integration of an open-source Arduino microcontroller. The final challenge in system design was the microreactor itself. The reactor was designed from the “bottom-up” to ensure optimal fluidic and thermal performance supported with both computational and experimental evidence. Overall the system was designed in such a way as to allow for automated experimentation using sensitive chemistries with in situ analytics integrated with the microreactor platform.

**Data Collection and Analysis**

Upon verifying reactor performance, a fractional factorial experimental design was used to test the effects of the concentration of monomer, activator and catalyst, with two additional experiments being performed to verify model fit. In total these seven experiments generated (with reactor rinses) about 10 grams of chemical waste, a two-to-three order of magnitude reduction form traditional experiments. The footprint of the experiment was contained to a nine-square foot area in a fume hood, again smaller than in a traditional experimental setup.

The reactor performed as designed, generating a series of exotherms with both dimensional and temporal resolution within the reactor. These exotherms were then used in conjunction with an energy balance for reacting laminar flow in a microchannel to generate plots of monomer concentration versus position in the reactor, as can be seen in Figure 5a. Differences can be observed between curves operating with the same initial hexene concentration. These curves show the rate at which 1-hexene was polymerized, allowing for the deduction of the catalytic productivity. As a next step the catalytic productivity was computed, defining how much polymer could be produced per unit of catalyst per hour. In Figure 5b it is observed how the catalytic productivity changes with changing reaction conditions. Finally, a series of ANNs were generated based off the experimental results in an effort to model the catalytic productivity throughout the experimental space. The results of this training in the form of Root Mean Square Error (RMSE) percentage over the dataset can be seen in Figure 3 of the supplemental information, ranging over both training method and the number of hidden layer neurons. The one step secant backpropagation (OSS) training algorithm with a feedforward network consisting of input layers, two hidden layers with 5 neurons each and an output layer. The OSS algorithm was predicted to
have the best representation because it leverages the benefits of both quasi-Newtonian and conjugate gradient algorithms. Neural networks were used as opposed to polynomial fits due to the ease of adaptability to new experiments and input/output parameters. In the case presented here the inputs consisted of concentration parameters, but the architecture of the network can be easily adapted to include other inputs including ambient temperature, flow parameters, and adaptations for different reactants. The network can also be rather easily updated using reinforcement learning to adapt to different alpha-olefin polymerization reactions. The network was designed to output the catalytic activity, a techno-economic parameter used to determine how much polymer is made per quanta of catalyst per quanta of time. During network initialization 70% of the experimental data was randomly chosen for training, with the remaining being used equally for testing and validation. Regularization and normalization were not used, as input data and output is fairly consistent between runs and is chemically is not expected to vary significantly in different trials. Raw data from the thermal camera was processed through ICI’s proprietary libraries which provided nonuniformity correction and autocalibration. For additional details on network training please see the Supporting Information.
Figure 5: (a) Experimental hexene concentration plots derived from the thermographic data showing the seven experiments performed in the experimental trial. (b) Catalytic productivity (grams of polymer / (mol(Zr) • mol (1-hexene) • h)) of the SBI(Zr)Me₂ catalyst from the different experimental profiles seen in panel (a). The error bars are the differences in analyzed exotherm between frames in flow over the course of the experiment, while the legend shows the type of concentration used in each trial.

ANN analysis

As the final component of the investigation a neural network was trained and used to compute the catalytic productivity over a broad range of literary plausible points within the reaction space. This methodology presents a way to efficiently visualize the reaction space topology for complex catalytic cycles with a minimum number of experiments. By training a neural network with a limited amount of experimental data results for similar conditions can be theorized over a user-selectable mesh granularity. As the dimensionality of the systems is increased, the computational intensity of the ANN simulations is not significantly impacted. The results of the ANN-based computation can be seen in Figure 6 with the first row showing the reaction space over a range of activator concentrations, the second row over monomer concentrations and the third row over catalyst concentrations. It is observed that catalytic productivity increases as activator concentration increases. As monomer concentration increases catalytic productivity tends to decrease, with a maximum being observed at high concentrations of activator and mid-range concentrations of catalyst. This data is potentially comparable to the trends seen in Table 2 of Moscato et al. 22. This is also consistent with the reaction mechanism because as
the concentration of monomer goes up the prevalence of vinylene and vinylidene termination mechanisms may increase, and at high catalyst concentrations the activity per gram catalyst is inherently lower due to the inverse relationship. As the catalyst concentration increases, the catalytic productivity decreases as expected since productivity is an inverse function of catalyst concentration. Finally, it is observed that to maximize the catalytic productivity high concentrations of activator should be used with lower concentrations of monomer and catalyst.
Figure 6: (top) Reaction space topology simulated from the ANN trained based on experimental data with the top row showing how the reaction space changes with changing activator concentration, the middle row showing the change with monomer concentration and the bottom row with catalyst concentration. (bottom) Maximum catalytic productivity under varying activator, monomer and catalyst loadings.

Conclusions

Semi-autonomous microfluidic platforms integrated with in-situ thermography may be used in conjunction with fitted neural networks in order to better understand catalytic cycles for homogeneous polymerization
reactions. It was shown that a metalloocene-catalyzed polymerization can be performed in a machine-assisted microreactor, the results quantified using an IR camera, interpreted using an energy balance and used to train an ANN. The ANN may then in turn be used to visualize the reaction space with a higher resolution than would otherwise be possible using traditional experimentation. The use of ANNs as opposed to linear, exponential or natural logarithmic models is that an ANN is independent to the physical behavior in the system and its implementation does not require an *ab initio* model. The reaction space for an industrially and academically relevant homogeneous metalloocene polymerization and the behavior towards varying concentrations of reactants was investigated. It was demonstrated using a combination of semi-automated experimentation and neural network analysis that there is a theoretical maximum catalytic productivity with respect to catalyst, monomer, and activator concentrations within the experimental space investigated. It was further determined that the one-step secant backpropagation neural network training method using 5 hidden layer neurons provided the highest fidelity and plausible fit because the derivative of the performance vector is calculated at each step and a new search direction is chosen.

Overall this study demonstrated that high-throughput microfluidics can be aided by Machine Learning algorithms for the investigation of complex chemical reactions. This opens doors to new types of research, primarily the “robotic chemist”, increasing throughput, data fidelity, and the efficiency of experimental campaigns. Future work could incorporate statically-based Monte Carlo design algorithms to aid in understanding the relationships between parameters. Depending on the use of the experimental results and knowledge of the underlying model other numerical fitting techniques may also be used. Performing reactions at the microscale with automation reduces the amount of energy input and chemical waste generated while also increasing safety because any failure in the reaction system is small and contained. Finally, the study aimed to contribute knowledge to on-line learning for complex systems, as the training methodology could be applied to other chemical, mechanical, and electric systems.

In the future, the methodology presented here may also be used to investigate other catalyst systems where a thermal signature may be expected including other polymerizations, exothermic biochemical transformations, and catalytic breakdown of harmful emissions including SOx and NOx compounds. This experimentation lays
the groundwork for the ability to predict optimal catalytic performance conditions autonomously. Optimization of industrially-relevant catalysts or catalyst/activator pairs may be accomplished by combining the neural network analysis with optimization techniques such as technoeconomic model minimization or genetic algorithms. Additionally, the high resolution ANNs can be combined with various topology analysis techniques to design new experiments. This AI methodology and the design of machine-assisted microreactors reduces the amount of chemical waste and energy input while enhancing the time-to-actionable-data and the resolution of reaction space topology.

**Author contribution statement**

Conceptualization: R.L.H.; Data curation: B.A.R.; Formal analysis: B.A.R. and A.S.S.; Funding acquisition: R.L.H.; Investigation: B.A.R. and A.S.S.; Methodology: B.A.R. and N.J.F.; Project administration: B.A.R. and R.L.H.; Resources: R.L.H.; Software: B.A.R., A.S.S., and N.J.F.; Supervision: R.L.H.; Validation: B.A.R. and A.S.S.; Visualization: B.A.R., A.S.S., and R.L.H.; Writing – original draft: B.A.R. and A.S.S.; Writing – review & editing: R.L.H. Corresponding: R.L.H.

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Combining automated microfluidic experimentation with machine learning for efficient polymerization design

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\textbf{Methods}

The reaction platform integrates an upstream manifold and mixing section, a displacement pump with reservoirs, an IR-transparent reactor, a thermal control system and an IR camera. The purpose of this system is to deliver a continuously variable experimental composition to the reactor, while also controlling mixing and dispersion through adjustable flowrate.

The reactor was fabricated by photopolymerization of VeroClear\textsuperscript{TM} resin (Stratasys, Rehovot, Israel) on an Objet30 Pro\textsuperscript{TM} printer with a dimensional accuracy of 16 \(\mu\text{m}\) with a tensile strength of at least 50 MPa. The top surface of the reactor was composed of Poly IR\textsuperscript{®} 1 (Fresnel Technologies, Fort Worth TX). After printing, the reactor was first cleaned in a sodium hydroxide bath (2\% solution, under sonication, 40 \(^\circ\text{C}\), overnight), then repeatedly rinsed with toluene, to remove any organic residues, and deionized (DI) water before being dried under filtered nitrogen. The IR film was cleaned with toluene and plasma etched for one hour. The reactor channels were masked off with hot wax where the top and bottom surfaces of the reactor were bonded using Loctite\textsuperscript{®} 406\textsuperscript{TM} ethyl cyanoacrylate adhesive. The assembly was then placed into a hydraulic press under 440 N of force for fifteen minutes. Finally, the device was exposed to UV light overnight. The device was then heated to 50 \(^\circ\text{C}\) to melt the wax, and rinsed...
repeatedly with toluene, acetone and DI water before being dried with nitrogen. An overview of the reactor geometry can be seen in Figure 1.

![Figure 1: CAD sketch of reactor dimensions, with units in mm](image)

Reagents were prepared in a glovebox operating at < 1 PPM O₂ and transferred in gastight syringes to the experiment. The syringes were then connected to a 6-inlet (Polytetrafluoroethylene) PTFE manifold (Cole-Parmer® EW-01356-17) which is connected to a dosing pump (Cole-Parmer® EW-73120-38). The dosing pump fed into a 1.5 mL reservoir.
(Elveflow® Eppendorf® XS-2) which was also connected to an Elveflow® OB1 pump. The reagents would then flow through the reactor to an output manifold which allows for sampling. All fluidic connections were made using 1/32 ID PTFE Teflon® tubing and the reactor was enclosed in a vacuum chamber to prevent IR interference and heat loss. During the beginning of a trial the respective manifold would be triggered, after which the dosing pump would transfer a preset volume of fluid to the reservoirs. The OB1 pump would then push this fluid through the reactor system using displacement via UHP N\textsubscript{2}. This allowed for mixing different ratios of reagents in real time and for the application of automation.

Due to the highly temperature-dependent nature of the metallocene polymerization catalysts, it necessary to provide a high degree of thermal control. This was provided by two 61-watt Marlow® TR060-6.5-40 L thermoelectric modules connected to an Eaton D96115ACZ3 solid-state relay driven by an ATmega 2560 Arduino® at ~490 Hz and 8-bit resolution. Thermal contact with the reactor was provided by a Protonix Series 7 thermal compound. Heat was dissipated from the thermoelectric modules through a liquid cooling block to a 360 mm radiator with 3 120 mm fans operating at 1650 RPM, a small expansion tank, and a 12 volt circulating pump. The system is constructed in such a way as to enable either elevated temperature operation through switching the polarity of the thermoelectric modules, or cryogenic operation by replacing the radiator with a chiller.

Monitoring and control of the experiment were accomplished using a calibrated infrared camera (ICI® 9640P) communicating via USB to MATLAB® R2019a using a proprietary ICI® library. Each frame from the thermal camera was stored as a 640x480 matrix of double precision values which was easily amenable to numerical filtering and analysis. Fluidic control was accomplished through LabVIEW® 2018 along with proprietary VI libraries from Elvesys®, with
a screenshot of the VI visible in Figure 1. Control of the feed solenoids was accomplished through a ATmega2560 Arduino® microcontroller coupled with a bank of relays switching 12 volt DC from a generic 300 watt ATX-style power supply. All power to the system is interlocked through a 120 volt, 30 amp electromechanical relay with an emergency disconnect button with all chemical-handling components being inside of a fume cabinet. Electrical interconnections are made through a Redco Audio® (Stratford, CT) snake box and shielded Cat5e cable.

The (SBI)ZrMe₂ (also known as rac-Me₂Si(Ind)₂-ZrMe₂) was purchased from MCAT GmbH, chlorobenzene (CAS 108-90-7), toluene (CAS 108-88-3) and 1-hexene (CAS 592-41-6) were purchased in anhydrous form along with B(C₆F₅)₃ (CAS 1109-15-5) from Sigma-Aldrich (St. Louis, MO).
Residence time distribution studies were carried out using a constant flow of water with acetone as the tracer. Fluid flow was provided by a Harvard Apparatus® PhD Ultra 2000 syringe pump and injection was performed using an Idex® 8125 Manual Injection Valve with a 50 µL injection volume. Detection of acetone in the reactor outlet was accomplished using an Ocean Optics® DH-2000-BAL UV-VIS-NIR light source coupled with an Ocean Optics® FLAME-S-UV-VIS-ES spectrometer measuring between 200-850nm with a 600/300 grating. Results of the RTD experiments can be seen in Table 1.

Table 1: RTD results showing the flowrate, Bodenstein number, and dispersion coefficient for the reactor.

| Flow Rate, (µL/min) | Mean Residence Time, τ(s) | Bodenstein Number, \( Bo = \frac{Re \times Sc}{\frac{ud_t}{D}} \) | \( \frac{L}{d_t} \) | Dispersion Coefficient, D (cm²/s) |
|---------------------|---------------------------|-------------------------------------------------|-----------------|-----------------------------|
| 185                 | 23.0745                   | 22.02                                           | 166.079         | 5.483x10⁻⁵                   |
| 350                 | 15.2696                   | 51.17                                           | 166.079         | 1.669x10⁻⁴                   |
| 515                 | 10.6609                   | 75.29                                           | 166.079         | 3.4797x10⁻⁴                  |

\( Re \) is the Reynolds Number, \( Sc \) is the Schmidt Number, \( u \) is flow velocity, \( d_t \) is hydraulic diameter, \( L \) is length of the channel.

Design of experiments was performed using MATLAB ® 2019a and the fraction factorial design generator function. This function was used to generate a four factor two level design accounting for the concentrations of catalyst, monomer and activator along with the reaction temperature to aid in the development of the 4D experimental topology.
Neural network training was performed using MATLAB® 2019a and the Deep Learning Toolbox. To determine the optimal training algorithm, a loop was run in which networks were trained using Levenberg-Marquardt (Damped Least Squares), quasi-Newton backpropagation, Resilient backpropagation (RProp), Scaled conjugate gradient backpropagation, Conjugate gradient backpropagation with Fletcher-Reeves updates, Conjugate gradient backpropagation with Powell-Beale restarts, Conjugate gradient backpropagation with Polak-Ribière updates, and one-step secant backpropagation methods with between one and one hundred neurons. Each network was trained ten times and the average Root-Mean-Squared Error percentage was computed and recorded. From visual analysis of the performance plot, the optimal network architecture was selected for further use in the study, shown below in figure 3.

In training the neural network, many things were taken into consideration. The model took into account the concentrations of all the reactants in the system, but is built in such a way that other parameters of interest such as temperature, turbulence, etc. can be taken into account. The output data consisted of the catalytic activity, a techno-economic parameter which takes into account both the amount of polymer produced and amount of catalyst used. Training was performed from the seven experiments performed with 71% of the points being used for training and the rest for validation. Other fitting methods such as polynomial fits were attempted, but resulted in less robust models which did not accurately reflect the kinetics of the system. A particular advantage of ANNs is the ability to easily update the network using reinforcement learning based off of new data in an on-line fashion. No data pre-processing was performed because the input data was consistent between all trials. The IR camera used had a built-in pre-processing algorithm for non-uniformity correction and autocalibration (see ICI documentation). The network was a single layer feed-forward type. Testing for overfitting was done by testing it
on experimental and plausible values and making sure there was data consistent with literature with no sharp gradients and erratic behavior and results.

Details of the network used are:

- **Dimensions:**
  - Number of inputs: 1 array
    - Concentration of catalyst
    - Concentration of monomer
    - Concentration of activator
    - Feed temperature
    - Flow velocity
  - Number of hidden layers: 2
  - Number of outputs: 1 double precision
    - Catalytic activity \( \frac{\text{grams polymer}}{\text{moles monomer} \cdot \text{moles catalyst} \cdot \text{hour}} \)
  - Number of input delays: 0
  - Number of feedback delays: 0
  - Number of weight elements
  - Number of weight and bias values: 31

- **Hidden layer activation function:** tanh
- **Output layer activation function:** linear

- **Functions**
  - Adapt function: adapt weight and bias values
  - Derivative function: calculate derivative from outputs to inputs using chain rule
  - Divide function: divide targets randomly
    - Training ratio: 70%
    - Validation ratio: 15%
    - Test ratio: 15%
  - Performance function: Mean Square Error
  - Performance parameters
    - Regularization: 0
    - Normalization: none

- **Training function:** One Step Secant Backpropagation (OSS)

- **Callable Network methods**
  - Adapt: update the network training from new results
  - Configure: adjust the inputs and outputs
  - Gensim: generate a Simulink model
  - Init: reinitialize the weights and biases
  - Perform: calculate network performance
  - Sim: evaluate the outputs of a network given a set of inputs
  - Train: train the neural network
  - View: view a visual representation of network layers
Figure 3: Investigation of the fit fidelity of different training methods with different numbers of hidden layer neurons. One step secant with 1 hidden layer of 5 neurons was selected for the final network architecture with root mean squared error used over the training sets. Training methods: 1 = Levenberg-Marquardt (Damped Least Squares), 2 = quasi-Newton backpropagation, 3 = Resilient backpropagation (RProp), 4 = Scaled conjugate gradient backpropagation, 5 = Conjugate gradient backpropagation with Fletcher-Reeves updates, 6 = Conjugate gradient backpropagation with Powell-Beale restarts, 7 = Conjugate gradient backpropagation with Polak-Ribière updates, 8 = One-step secant backpropagation.

Calculations

To begin the calculations, the rate of 1-hexene consumption, $-r_A$, can be calculated using the design equation from plug flow reactor:

$$-r_A = F_A \frac{dX}{dV} \quad (1)$$
where \( r_A \) is the rate of reaction, \( F_{A0} \) is the initial molar flowrate, and \( \frac{dx}{dv} \) is the change in conversion over the change in volume.

To calculate conversion of 1-hexene an energy balance equation was required. The equation for the change in temperature over change in volume down the length of the reactor is:

\[
\frac{dT}{dV} = \frac{Q_g - Q_r}{\sum F_i C_{pi}} (2)
\]

where \( Q_g \) represents the rate heat generation, \( Q_r \) is the rate of heat removal by conduction of the walls of the reactor, and \( F_i \) is molar flowrate and \( C_{pi} \) is the specific heat capacity of each substance.

The heat generated, \( Q_g \), is represented by:

\[
Q_g = r_A \Delta H_{Rx} = F_{A0} \frac{dx}{dv} \Delta H_{Rx} (3)
\]

where the rate of reaction, \( r_A \), is substituted by the design equation for a plug flow reactor from equation 1.

The heat removed from the reaction, \( Q_r \), is calculated by the equation:

\[
Q_r = \frac{UA}{V} (T - T_a) (2)
\]

where \( U \) is the overall heat transfer coefficient, \( A \) is the surface area of the reactor channel divided by the channel’s volume \( V \), and \( T_a \) is the ambient temperature of the reactor which is assumed to be constant.

Substituting equations (3) and (4) into equation (2), we get:

\[
\frac{dT}{dV} = \frac{F_{A0} \frac{dx}{dv} \Delta H_{Rx} - \frac{UA}{V} (T - T_a)}{\sum F_i C_{pi}} (5)
\]
Which can be rewritten and both sides multiplied by \( dV \) to introduce:

\[
\sum F_i C_{Pl}dT = F_{A0}\Delta H_{Rx} dX - \frac{UA}{V} (T - T_a) dV
\]  

(6)

Integrating down the length of the reactor using the intervals of temperature from \( T_0 \) to \( T \), conversion from 0 to \( X \), and volume from 0 to \( V \) yields:

\[
\sum F_i C_{Pl}(T - T_0) = F_{A0}\Delta H_{Rx} X - UA(T - T_a)
\]  

(7)

Where the equation can finally be rearranged to solve for conversion as:

\[
X = \frac{\sum F_i C_{Pl}(T - T_0) + UA(T - T_a)}{F_{A0}\Delta H_{Rx}}
\]  

(8)

Numerical methods exist to obtain rate constants for initiation and propagation, \( k_i \) and \( k_p \) respectively, using a nonlinear least squares regression of the apparent rate of conversion of 1-hexene, \( \frac{dX}{dV} \), down the length of the microreactor.

The rate law (shown in equation 9) used assumes 1st order dependence of each reactant. The concentration of growing chains of any length, \( n \), is represented by \([Zr \cdot \text{Hexene}_n]\). Active, but not yet initiated, catalyst site concentration is represented as \([Zr]\).

\[
-r_A = k_p [\text{Hexene}][Zr \cdot \text{Hexene}_n] + k_i [\text{Hexene}][Zr]
\]  

(9)

The approximation \( \frac{\Delta X}{\Delta V} \approx \frac{dX}{dV} \) is used to get a rough estimate for the change in conversion down the length of the reactor by taking measurements of many closely spaced points.

The equations (8) and (9) are combined to get the function that the nonlinear regression fits:

\[
\frac{dX}{dV} = \frac{k_p [\text{Hexene}][Zr \cdot \text{Hexene}_n] + k_i [\text{Hexene}][Zr]}{F_{A0}}
\]  

(10)
The concentrations of each reactant are calculated using the rate constants being fitted and the initial concentrations plugged into a simultaneous ODE solver. The ODE solver finds numerical solutions to the three differential equations we use to describe the largest contributing factors to the overall reaction. The most important differential equations are:

\[
\frac{d[\text{Hexene}]}{dV} = -\frac{k_p[\text{Hexene}][\text{Zr} \cdot \text{Hexene}_n] + k_i[\text{Hexene}][\text{Zr}]}{v_0} \tag{11}
\]

\[
\frac{d[\text{Zr} \cdot \text{Hexene}_n]}{dV} = \frac{k_i[\text{Hexene}][\text{Zr}] - k_d[\text{Zr} \cdot \text{Hexene}_n]}{v_0} \tag{12}
\]

\[
\frac{d[\text{Zr}]}{dV} = -\frac{k_i[\text{Hexene}][\text{Zr}]}{v_0} \tag{13}
\]

where \(v_0\) is the volumetric flow rate and \(k_d\) is the death rate constant which is chosen carefully for the fitting function to converge. These rates correspond to the reaction steps:

\[
\text{Activated Zr + Hexene } k_i \rightarrow \text{ Zr} \cdot \text{Hexene}_1
\]

\[
\text{Zr} \cdot \text{Hexene}_n + \text{Hexene } k_p \rightarrow \text{ Zr} \cdot \text{Hexene}_{n+1}
\]

The assumption is made that all the catalyst is quickly activated relative to the reaction rate.

The nonlinear regression function converges when given the initial guesses \(k_i = 0.1, k_p = 1\) and \(k_d = 0.001\) which is consistent with the ratios of those values found in literature.
