Catalyst Immobilization Techniques
for Continuous Flow Synthesis
Kevin D. Nagy

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Catalytic processes are ubiquitous in both research and industrial settings. As continuous flow processes continue to gain traction in research labs and fine and pharmaceutical chemical processes, new opportunities exist for implementing previously difficult catalytic transformations. The major goal of this thesis is to expand and evaluate techniques for immobilized catalyst systems relevant to continuous flow. Fundamental studies in characterizing mixing, dispersion, and residence time distributions in small scale continuous flow systems are also presented. Given the numerous benefits associated with studying chemical processes at small length scales, microfluidic devices are the tool of choice for most studies in this thesis.

Thermomorphic solvents offer the potential for homogeneous catalytic processes with biphasic catalyst recovery and recycle. A major limitation of these processes is the number of synthetically useful thermomorphic solvent combinations demonstrated in literature. A screening program using the modified UNIFAC (Dortmund) activity coefficient model to evaluate phase splitting behavior has been developed to predict thermomorphic behavior. Calculation of 861 binary solvent combinations results in 43 potential thermomorphic and 44 biphasic solvent combinations. Extension of the program to ternary solvents resulted in a new class of ternary solvents that display thermomorphic behavior with tunable critical solution temperatures. Evaluation of thermomorphic processes as a general method is presented.

Traditional catalyst immobilization techniques rely on covalent grafting and are well suited to continuous flow processing due to the strong interactions of the catalyst to the support. Fluorous physisorption, which relies on interactions between a fluorous support and a fluorous-tagged catalyst, is characterized and presented as an immobilization technique for flow chemistry. The use of a fluorous-tagged Co(III)-salen catalyst to effect the ring opening of epoxyhexane with water is presented. Application of the platform to the ring closing metathesis of N,N-diallyltosylamide using a fluorous-tagged Hoveyda-Grubbs metathesis catalyst results in significantly accelerated loss of activity over time compared to the salen catalyst.

Use of continuous flow selective adsorption reactors to enhance catalytic processes is presented. Continuous feeds of a homogeneous catalyst into a sorbent where the catalyst displays an affinity for the sorbent results in accumulation of the catalyst in the packed bed. The net effect is an enhancement in turnover frequency and turnover number relative to homogeneous flow. Application of this platform to a Lewis acid catalyzed Diels-Alder reaction results in an order of magnitude improvement in turnover frequency compared to batch and homogeneous flow.

Thesis Supervisor: Klavs F. Jensen
Title: Warren K. Lewis Professor of Chemical Engineering
Professor of Materials Science and Engineering
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I dedicate this thesis to my parents, Bert and Laura, and my sister, Sarah, who have loved and supported me longer than I can remember.
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Ch 1. Background, motivation, and objectives

1.1 Importance and fundamentals of catalytic processes

Some of the most important technological advances of the 20th century were catalytic processes for large scale fuel and commodity chemical synthesis. Since the discovery of the Haber-Bosch process in 1909, the catalytic fixation of nitrogen and hydrogen to produce ammonia has enabled worldwide production of low cost fertilizers. Fluidized catalytic cracking, a widely used process to break apart long chain alkanes, was developed in the 1940s and is responsible for production of a significant fraction of the world’s gasoline. The development of Ziegler-Natta and related catalysts for the bulk production of polymers in the second half of the twentieth century has enabled numerous advances ranging from lighter planes and cars to cheap soda bottles. These advances, and numerous others, highlight the impact catalysis has made on the modern world.

Catalytic processes work either by directly lowering the activation energy of a reaction or by enabling alternate pathways to proceed. As the addition of catalysts directly impacts the kinetic rate, useful metrics to compare catalysts are turnover frequency (TOF) and turnover number (TON). The turnover frequency is the rate of reaction of generic species $A$ with concentration $A$ normalized to the catalyst concentration $C$ (equation 1.1), whereas the turnover number is the amount of product formed normalized to the amount of catalyst (equation 1.2). The two relationships are related by either differentiation or integrating (equation 1.3). An erroneous manner in which the turnover frequency is frequently reported is by dividing the TON by the total reaction time, which neglects the rate dependence. Also worth consideration is whether a TON or TOF should be calculated based on product yield or conversion of starting material, as
the value reported may be slightly different in the case of unwanted side reactions; a TON or TOF based on yield should be preferred.

\[
TOF = \frac{\text{mol reacted}}{\text{mol catalyst} \times \text{unit time}} = \frac{1}{C} \frac{dA}{dt}
\]

(1.1)

\[
TON = \frac{\text{mol reacted}}{\text{mol catalyst}}
\]

(1.2)

\[
TON = \int_0^T OF dt
\]

(1.3)

Catalytic processes are also extremely important for the production of fine and pharmaceutical products. In addition to enabling a wide range of reactions necessary to create complex molecules, several important catalytic reactions facilitate convergent syntheses\(^6\), which is an important strategy to augment the yields of molecules requiring multiple steps\(^7\)\(^-\)\(^9\). Many of the most common and important catalytic reactions for joining complex fragments rely on palladium; selected reactions appear in Table 1.1.

Despite being so important to the fine and pharmaceutical industry, catalytic processes also pose problems. Depending on the chemical reaction and catalyst being used, the cost of the ligand or catalyst can represent a significant fraction of the total catalyst cost. Furthermore, metal contamination is critically important in pharmaceutical products, with acceptable metal contents as low as 5 ppm\(^10\). These factors may necessitate costly separation steps to remove residual metals. Traditional aqueous workups and column chromatography may be sufficient for bench scale purifications; however, use of distillations\(^10\), multi-step extractions\(^11,\ 12\), or the addition of solid sorbents, either by addition of particulates to a batch of material\(^10,\ 13\) or through fixed bed adsorption\(^14\), may be necessary at production scales. Considerations of these factors indicate that the use of immobilized catalyst systems to reduce both catalyst consumption and product impurity profiles are attractive processing techniques.
Table 1.1 – Selected efficient Pd-catalyzed reactions for joining large molecules\textsuperscript{15-20}.

<table>
<thead>
<tr>
<th>Name</th>
<th>Characteristic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzuki-Miyaura coupling</td>
<td><img src="image1" alt="Diagram" /></td>
</tr>
<tr>
<td>Stille cross coupling</td>
<td><img src="image2" alt="Diagram" /></td>
</tr>
<tr>
<td>Negishi coupling</td>
<td><img src="image3" alt="Diagram" /></td>
</tr>
<tr>
<td>Buchwald amination</td>
<td><img src="image4" alt="Diagram" /></td>
</tr>
<tr>
<td>Heck reaction</td>
<td><img src="image5" alt="Diagram" /></td>
</tr>
<tr>
<td>Sonogashira coupling</td>
<td><img src="image6" alt="Diagram" /></td>
</tr>
</tbody>
</table>

1.2 Traditional catalyst immobilization techniques

Perhaps the most common technique for catalyst immobilization involves covalent attachment of a catalyst to a support. Numerous catalysts, with applications ranging from polymerizations\textsuperscript{21} to the selective reduction of ketones\textsuperscript{22}, have been successfully developed using these schemes (Figure 1.1). While the permanence of this approach to catalyst immobilization is attractive, significant disadvantages include the additional complexity of catalyst preparation\textsuperscript{23} and potential mass transfer limitations to sites located within pores\textsuperscript{24}. Furthermore, deactivated
catalysts can be difficult to regenerate, should regeneration even be possible. Well designed heterogeneous catalysts remains an active area of research that will no doubt see continued interest in the future. Immobilization of catalysts on heterogeneous supports can also occur through non-covalent means; an overview of these techniques is presented in chapter 5 of this thesis.

![Figure 1.1 - Selected examples of heterogeneous catalyst immobilization using covalent attachment. Top: Covalently grafted catalysts. Bottom: Originally reported homogeneous catalyst. PS: polystyrene, Cy: cyclohexane, tBu: tert-butyl, and Ar: 2,6-diisopropyl benzene.](image)

Immobilization of homogeneous catalysts can be realized by the addition of a phase selective moiety and operation under biphasic conditions. Catalyst recovery can be achieved by simple liquid-liquid separations, and recycle can be implemented by addition of fresh substrate. This technique thus trades mass transfer resistance from a homogeneous liquid to a heterogeneous site for interfacial mass transfer resistance. The most common example of phase selective catalyst immobilization involves use of sulphonated phosphine ligands, though poly(ethylene glycol), fluorous tags, and ionic liquids have also been used. A recent development in biphasic catalyst recovery involves the use of thermomorphic processes. These processes use solvent combinations which undergo temperature dependent phase changes to enable homogeneous processing conditions while retaining the ability to separate and recover catalysts under biphasic conditions.
Mechanistic understanding of catalytic processes is important for understanding whether catalyst immobilization will be an effective strategy. Numerous studies using Pd nanoparticles to catalyze Suzuki\textsuperscript{41-44} and Heck\textsuperscript{45-48} reactions are published nearly every year, despite strong evidence that the catalytic activity in these systems is from leached palladium\textsuperscript{49-52}. Our own brief foray into this area demonstrated no advantage for using nanoparticles for a Heck reaction (Figure 1.2).

Figure 1.2 – Comparison of homogeneous and heterogeneous Pd-sources at 0.05 mol\% loading for the Heck reaction of 4-iodo methoxybenzene with ethylacrylate. Nanoparticles were prepared by Dr. Victor Cabeza of the Jensen group.

While full conversion was achieved in all cases using 0.05 mol\% Pd (TON: 2000), conversion took significantly longer when using the nanoparticles compared to standard commercially available palladium sources, such as palladium diacetate (Pd(OAc)\textsubscript{2}) or tris(dibenzylideneacetone) dipalladium(0) (Pd\textsubscript{2}(dba)\textsubscript{3}). The induction period when Pd\textsubscript{2}(dba)\textsubscript{3} was used corresponds to dissociation of free Pd(0) from the stabilizing dibenzylideneacetone ligand. Similarly, the induction period when using the nanoparticles indicates \textit{in situ} catalyst formation.
from the heterogeneous Pd-source was rate limiting. This study demonstrates immobilization of Pd-nanoparticles on a heterogeneous support would not be an effective technique.

1.3 Microreactors for studying catalytic processes†

The advantages of microreactors for studying flow chemistry are well documented\textsuperscript{53-57}. These devices have characteristic dimensions of $<1$ mm but are more typically within 50-500 micron; the small length scales enable both rapid diffusion-based mixing\textsuperscript{58,59} and high interfacial areas for multi-phase applications\textsuperscript{60}. Microfluidic devices can be made of low cost capillary tubes and HPLC fittings; however, significantly more complex devices containing integrated valves\textsuperscript{61-63}, pumps\textsuperscript{64,65}, and separations\textsuperscript{66,67} can be made from silicon\textsuperscript{68}, stainless steel\textsuperscript{69}, ceramics\textsuperscript{70,71}, glass\textsuperscript{72}, poly(dimethyl siloxane)\textsuperscript{62,73-75}, or poly(tetrafluoroethylene)\textsuperscript{76} (Figure 1.3).

![Figure 1.3 - Complex integrated microfluidic devices. Top left: Onchip multistep synthesis of radiolabeled imaging probes\textsuperscript{65}. Top right: Integrated formulator for protein crystallization screening\textsuperscript{63}. Bottom: SlipChip for combinatorial screening\textsuperscript{77}.

Material of construction plays a large role in the characteristics of a microreactor. Microreactors with high heat conductivity, such as those made from silicon or ceramics, facilitate both extremely exothermic reactions and reactions requiring high temperatures\textsuperscript{78,79}. The small thermal mass of the fluidic elements enables near instantaneous heating and cooling;

temperature drops > 200°C have been achieved over the distance of only a few millimeters using so-called “halo etch” microreactors (Figure 1.4)\textsuperscript{80}.

Figure 1.4 – Halo-etched reactors enable high temperature-high pressure reactions. Top left: Reactor schematic\textsuperscript{81}. Top middle: Chip holder schematic\textsuperscript{80} Top right: Photograph of packaged device\textsuperscript{80}. Bottom: Steady state temperature profile obtained using COMSOL 3.2\textsuperscript{82}.

Several microreactor designs allow operating pressures up to hundreds of bar\textsuperscript{72, 80, 83}. The combination of these properties enable reactions at extreme conditions\textsuperscript{69}, such as the epoxide aminolysis in THF at 195°C\textsuperscript{82, 84} and nanoparticle formation in supercritical solvents\textsuperscript{85, 86}.

Continuous flow operation and small volumes enable numerous experiments to be carried out quickly and using small volumes of material; a kinetic study comprising >100 experiments was performed by a single researcher in <24 hours\textsuperscript{82}. Computer controlled platforms coupled with inline analytics and feedback algorithms offer the potential to screen many reactions\textsuperscript{87-89},
optimize chemical processes without user input\textsuperscript{90, 91}, and rapidly obtain kinetic data using minimal amounts of material (Figure 1.5)\textsuperscript{92}.

Figure 1.5 – Automated experimentation represents some of the most promising applications for microfluidics.

The development of continuous separations using surface forces for multi-phase liquid-liquid and gas-liquid systems has enabled multi-step chemical transformations\textsuperscript{93-95}. Compared to the initial designs where fluid was contacted across microfabricated capillaries\textsuperscript{96}, the development of selective wetting membranes allows for higher throughputs and the potential to scale beyond the microscale\textsuperscript{66}. Furthermore, as these separations operate on the basis of differential pressure across the membrane, gas-liquid and liquid-liquid separations at high pressure can be achieved\textsuperscript{97}.

As the development of new catalytic processes continues, the ability to rapidly screen numerous reaction conditions using minimal amounts of material will be attractive. An overview of the current state of the art of catalytic processes in microreactors follows.
1.3.1 Homogeneous liquid phase processes

Microreactors coupled with inline analytics are ideal for performing high throughput catalyst screening and optimization due to the small catalyst quantities consumed during these processes. Weber and co-workers recently screened the activity of 18 different acid catalysts using 2.4 µg of material per experiment\(^7\). Inline UPLC was used for reaction monitoring, and the authors claimed studies using nanograms of materials were feasible.

McMullen and Jensen have developed a similar self optimizing platform and demonstrated the selective oxidation of benzyl alcohol to benzaldehyde using a chromium catalyst and a palladium catalyzed Heck reaction of a deactivated aryl chloride and alkene\(^{90, 91}\). The optimized experimental conditions for the Heck reaction could be directly scaled 50x to a meso-reactor with nearly identical performance. Most previous studies have observed that the throughput limiting step in these platforms is typically the analytical equipment, as the use of chromatographic separations introduces additional time delays in the system. Quantitative inline analytical techniques that do not require separation, such as in-line FTIR\(^98\) and flow NMR\(^99\), should enable increased experimental throughput.

The ability to precisely control fluid contacting time in continuous flow systems enables catalytic transformations of unstable species. Yoshida and co-workers have developed a number of reactions in this vein\(^{57}\). A recent example involved a sequential lithium-halide exchange reaction followed by a PEPPSI catalyzed Murahashi coupling reaction (Figure 1.6)\(^{100}\). The lithium-halide exchange, normally done at -78°C in batch, was complete in 2.6 seconds at room temperature, and the cross coupling results for several species gave good to excellent yields in 94 s at 50 °C with 5 mol% catalyst. Use of 1 mol% catalyst with p-bromoanisole resulted in significantly reduced yields (18% vs 93%) and significant amounts of a side product,
butylmethoxybenzene, which highlights the challenge of working with such unstable intermediates.

\[
\begin{align*}
\text{Br} & \quad \text{BuLi} & \quad \text{Li} & \quad \text{PEPPSI-SiPRBuLi} & \quad \text{Ph} \\
OMe & \quad \quad 0 \degree \text{C}, 2.6 \text{ s} & \quad \quad OMe & \quad \quad 50 \degree \text{C}, 94 \text{ s}
\end{align*}
\]

**Figure 1.6** – Murahashi cross coupling achieved using continuous flow technology.

### 1.3.2 Multi-phase liquid-liquid and gas-liquid catalytic processes

Continuous flow technology is excellent for studying high pressure gas-liquid reactions that are difficult or hazardous to run in batch. Furthermore, the high interfacial area makes microfluidic devices excellent tools for studying multi-phase chemistry. Gas-liquid mass transfer coefficients as high as 8.0 s\(^{-1}\) have been achieved\(^{101}\), which is two orders of magnitude higher than batch or semi-batch reactors\(^{102}\). In addition to reaction acceleration, increased mass transfer can change reaction selectivity, as demonstrated by the enhanced formation of \(\alpha\)-ketoamide in a Pd-Xantphos catalyzed aminocarbonylation reaction at elevated pressures in flow systems compared to batch\(^{103}\).

An interesting example highlighting many of these advantages comes from Stahl’s group, which in collaboration with Eli Lilly, recently developed a scalable protocol for the oxidation of secondary alcohols to ketones and aldehydes using a palladium catalyst and oxygen (Figure 1.7)\(^{104}\). The reaction time was reduced from 18 hours in batch to 45 minutes in a 5 mL (0.25” OD) tubular steel reactor under flow conditions using 30 psia oxygen. Furthermore, enhanced mixing in the flow system reduced the formation of palladium black, which was problematic in batch operations. Scale-up of 10 compounds at flow rates of 54 mmol substrate per hour using ~5% \(O_2\) at a total pressure of 500 psi was achieved in a 400 mL (0.5” OD) tubular reactor. The oxidation of 1-phenylethanol to acetophenone was demonstrated in a 7 L (0.375” ID) reactor at a
kilogram scale in near quantitative yield. Notably the residence times reported increased with scale – 45 minutes in the 5 mL reactor, 2.5 hours in the 400 mL reactor, and 4.5 hours in the 7 L reactor, though the authors stated direct scale-up by two orders of magnitude from the 7 L reactor was possible. The reduced space time yields are a direct result of reduced mass transfer at larger length scales and highlight the challenge of scaling multi-phase continuous flow processes.

Figure 1.7 – Pd-catalyzed oxidations of secondary alcohols to ketones under continuous flow conditions at a total system pressure of 500 psi.

Continuous flow catalyst recycling has recently been accomplished using molecular weight enlarged (MWE) catalysts in conjunction with nanofiltration membranes. A MWE triphenylphosphine derived catalyst was used in the hydroformylation of 1-octene, such that the substrate and product permeated the ceramic membrane but the metal-ligand complex was retained. The catalyst containing retentate was recycled for nearly 2 weeks before significant catalyst deactivation was observed, and a turnover number of 120,000 was achieved. The major disadvantage of nanofiltration is the high operating pressures required to force material through the nanofiltration membrane, though in this example, the separation pressure corresponded to the operating pressure.

In the case of liquid-liquid systems, use of phase selective ligands enable downstream separation and catalyst recycling, though surprisingly little work on catalyst recycling has been reported using continuous flow technology. Two such examples involve recycling palladium catalysts. Huck and Wootton performed Pd-catalyzed Suzuki couplings of aryl boronic acids and aryl bromides using a fluorous-aqueous system with a fluorinated guanidine ligand. The
catalyst was continuously recycled for three “cycles” with less than 2% Pd loss into the product. Early work by the Ryu group performed a solvent free Heck reaction using a low viscosity ionic liquid\textsuperscript{107}. The catalyst containing ionic liquid was continuously recycled ~5 “cycles” over 11.5 hours, which produced ca. 10 g/hour of butyl cinnamate in a 15 mL CYTOS CPC lab system. Continuous product and salt extractions were performed with good retention of the catalyst in the ionic liquid phase. In both of these cases, separations were accomplished via gravitational settling, and catalyst recycling was performed with an inline pump. The micro scale separations using capillary forces previously mentioned would have reduced holdup compared to the mL scale settling tanks used in these examples\textsuperscript{96}.

Organic-aqueous biphasic systems also enable flow processes for reactions that generate inorganic salt byproducts. Naber and Buchwald found that efficient mass transfer was critical in both batch and continuous Pd-catalyzed amination reactions of aryl chlorides and aryl amines\textsuperscript{108}. The use of both tetrabutylmmonium bromide as a phase transfer agent and a column packed with stainless steel beads were necessary to achieve high yields (Figure 1.8). Performing the reaction in capillary tubing or without a phase transfer catalyst resulted in significantly reduced yields. Furthermore, the use of different volume packed beds at a constant residence time demonstrated that either the mass transfer or hydrodynamics within the reactor were critical, as faster linear velocities resulted in improved yields. This technique has since been extended to Suzuki couplings\textsuperscript{94}.
1.3.3 Solid supported catalytic processes

The most common reactor design for solid supported systems is a fixed bed, where porous catalyst particles are retained in a chamber and the reaction solution passes over it. High catalyst loadings per unit volume may be achieved, which result in reduced residence times. Downstream purification steps to remove catalyst from the product are unnecessary, and unlike biphasic systems, liquid-liquid separations and pumps are not required for catalyst separation and recycle. Our group has developed a number of silicon devices that enable visual access\textsuperscript{109-112} for applications ranging from phosgene synthesis\textsuperscript{113} to kinetic analysis of hydrogenation catalysts\textsuperscript{97} (Figure 1.9).

A number of other research groups beyond our own have also investigated fixed bed reactors for catalytic processes\textsuperscript{114}. The commercial supplier Thales-Nano offers a number of catalyst cartridges for its H-cube platform; however, the company's main focus remains hydrogenations\textsuperscript{115,116}. The Ley group has performed a number of Pd-catalyzed reactions using heterogeneous palladium sources\textsuperscript{117-119}, though these reactions likely occur through homogeneous mechanisms as discussed in section 1.2. Monolithic supports developed by Andreas Kirschning\textsuperscript{120,121} and others\textsuperscript{122,123} offer an alternative to either silica or polymer bead supports.
Solid liquid catalytic systems suffer from a number of challenges at the microscale. Common polymeric supports, such as Merrifield resins, can swell in organic solvents. Swelling can potentially reduce access to catalytic sites while increasing pressure drop and can even cause brittle reactors, such as those made from glass or silicon, to fail. Furthermore, the smaller interstitial path lengths in packed beds prohibit reactions that produce solids, as sonication and other techniques to control particle growth and deposition are ineffective\textsuperscript{124, 125}. Lastly, solid supported catalysts that operate through so-called “boomerang” mechanisms, where the active species desorbs from the support under reaction conditions and re-adsorbs upon completion of the reaction, are poorly suited to flow conditions.

The high surface area to volume ratio of microreactor systems offers the ability to immobilize catalysts in other manners besides on beads. Impregnating microstructured features\textsuperscript{110} or even directly coating the surface of capillary tubing may be effective\textsuperscript{126, 127}. In certain cases, reactors can even be made of the catalytic material, as demonstrated by Bogdan and Sachs, who used copper tubing to catalyze azide-alkyne click reactions and synthesized a library of 30 triazoles in a few hours\textsuperscript{128}. The major advantage of these techniques compared to

---

**Figure 1.9 - Microfabricated devices for studying supported catalysts.** From left clockwise: High pressure gas-solid reactor\textsuperscript{109}. Gas-liquid-solid trickle bed reactor\textsuperscript{109}. Gas-liquid trickle bed reactor\textsuperscript{110}. Parallel packed bed with integrated temperature sensors\textsuperscript{112}. Porous silicon posts\textsuperscript{110}. Cross flow packed bed\textsuperscript{111}. 

---
packed beds is increased heat removal, as the amount of catalyst per reactor volume is significantly lower. Results obtained in these types of reactors will be challenging to scale as demonstrated below.

For capillary tubing, the surface area to volume ratio can be calculated by dividing the tube diameter by 4. Thus, 500 micron diameter ID capillary tubing has 8,000 m²/m³, whereas 1 mm diameter ID tubing only has 4,000 m²/m³. Conversely, the surface area to volume ratio in packed beds is determined as the product of the bulk density and surface area per mass. Commercially available silica gel has a bulk density of ~700 kg/m³ and surface area ranging from 450 to 600 m²/g, giving a surface area to volume ratio of 3.1-4.2x10⁸ m²/m³, a factor of 40,000-200,000 larger than surface coatings. Considering the surface area to volume ratio of non-porous 50 micron beads is 60,000 m²/m³, even low surface area supports will outperform surface coated tubes. Furthermore, the surface area to volume ratio of packed beds does not change as a function of bed diameter. While catalytic surface coatings will continue to be important for extremely exothermic reactions, such as combustion, their practical use in liquid phase organic transformations is limited for most industrial applications.

1.4 Specific thesis objectives and outline

Due to the importance of both catalytic and continuous flow processes for organic syntheses, the evaluation and implementation of novel catalyst immobilization techniques under flow conditions was the primary goal of this thesis. The secondary aim of the thesis was to extend the utility of microreactor technology for chemical synthesis applications. These results are presented in reverse order; the first portion of the thesis comprises fundamental studies in residence time distributions, dispersion, and mixing relevant to microreactor platforms, and the second half of the thesis evaluates thermomorphic processes and physical adsorption techniques.
for catalyst immobilization and recycle. The penultimate chapter describes a new concept for augment homogeneous catalytic processes through the use of continuous flow selective adsorption reactors. The last chapter summarizes the major contributions of the work.

Development of a means to evaluate catalyst retention under physical adsorption techniques was necessary, and inline UV-vis spectroscopy was identified as a suitable technique. The application of this platform to characterize flow patterns in single-phase liquid, multi-phase liquid-liquid, and multi-phase gas-liquid flows is discussed in chapter two of this thesis.

A summary of dispersion and mixing effects in flow systems is presented in chapter three of the thesis. These effects can have a significant impact on reactor behavior, and the ability to quickly identify the relative impact of each parameter on a flow system is presented. Both effects can be calculated using a system Fourier number, which is the ratio of the residence time in a flow system to the characteristic tranverse diffusion time. The techniques outlined in the chapter are demonstrated to improve throughput and selectivity of a previously reported glycosylation reaction.

The evaluation of thermomorphic processes as potential immobilization techniques for flow systems is the focus of chapter four. A major limitation to the technique was identified as an insufficient number of known synthetically useful solvents that display thermomorphic behavior. A screening program was written to predict new solvent combinations using activity coefficient models. The simulation resulted in the identification of several new thermomorphic solvent combinations, including ternary systems with tunable critical solution temperatures. Consideration of the limitations of thermomorphic processes is presented, and the technique is ultimately evaluated as being too constrained to serve as a general technique for catalyst immobilization and recycle under flow conditions.

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Investigation of fluorous physisorption as an immobilization technique under flow conditions is presented in chapter five of this thesis. The successful application of a fluorous-tagged salen catalyst to effect the ring opening of epoxides demonstrated the utility of the immobilization technique. The application of the platform to a fluorous-tagged metathesis catalyst resulted in loss of activity over time, which was determined to be from catalyst deactivation and not elution. A novel catalyst recycling scheme for these types of systems is also presented.

A proposed model for enhancing catalytic processes through the use of selective adsorption reactors is the focus of chapter six. The use of phase tagged catalysts in conjunction with adsorption beds is demonstrated to augment catalyst performance due to accumulation of the catalyst on the adsorbent bed. The technique is demonstrated using a fluorous-tagged Lewis acid catalyst to effect a Diels-Alder reaction with TOF enhancement of an order of magnitude compared to batch results. A second application to the fluorous-tagged metathesis catalysts presented in chapter five resulted in significantly enhanced behavior and the surprising discovery that non-fluorous tagged catalysts can also adsorb on fluorous supports. A mathematical model of the system is presented, as well as the potential advantages and limitations of the technique.

The major research contributions of this thesis are summarized in chapter seven, and comments on the future outlook for the field are presented.
Ch 2. A general platform for characterizing single-phase and multi-phase residence time distributions

2.1 Motivation

Choice of reactor model can have a large impact on chemical conversion within a flow system. The two extremes of flow reactor geometries are the continuous stirred tanked reactor (CSTR) and the plug flow reactor (PFR). Kinetic models for CSTR come from performing a macroscopic mass balance around the reactor and neglect mixing effects; the operating condition for a CSTR is assumed to be the outlet concentration. Conversely, kinetic models for plug flow reactors are derived through a shell balance, which results in axial concentration gradients and conversion as a function of length or residence time. The kinetic model for a plug flow reactor in the absence of volume changes is mathematically identical to a batch reactor. Both CSTRs and PFRs are advantageous for specific reaction types; as CSTRs operate at the outlet concentration, negative order reaction models proceed most quickly, whereas positive order reactions proceed more slowly. Conversely, the higher inlet concentrations make PFRs advantageous for positive order reactions. As most liquid phase organic transformations display positive order dependencies on concentration, the PFR model represents a desirable reactor type for flow processes.

In reality, different combinations of reactor configurations exist; multiple CSTRs in series can provide a reasonable approximation of PFR behavior, which can be useful for reactions that generate solids. Conversely, tubular flow reactors can deviate from plug flow behavior at low Reynolds numbers due to a parabolic velocity profile. Other potential causes of deviations from plug flow arise from maldistribution of flow through poorly packed fixed bed reactors, recirculation eddies due to geometry changes, or entrance and exit effects. Quantifying the
deviation from plug flow is important and has been generally termed dispersion; dispersion
effects can adversely affect both conversion and reaction selectivity.

A technique for characterizing the flow profile through a reactor involves performing
residence time distribution (RTD) measurements\textsuperscript{24,130}. This technique allows facile comparison
between different reactor geometries and configurations and enables determination of the
magnitude of deviation from plug flow behavior. This chapter outlines a general platform that
has been used for single phase and multi-phase RTDs and includes the physical setup and theory
used to analyze experimental results.

2.2 Review of theory of residence time distributions

Residence time theory is closely tied to the analysis of dispersion coefficients performed by
Taylor and Aris in the 1950s\textsuperscript{131,132}. The key transformation to arrive at the dispersion model
involves a change of coordinates in the convection-diffusion model for fluid flowing through a
tube from a stationary tube (equation 2.1) to a stationary mean fluid center point (equation 2.2).
The transformed continuity equation appears in equation 2.3.

\[
\frac{dC}{dt} = D \frac{d^2C}{dx^2} - u \frac{dC}{dx} \tag{2.1}
\]
\[
\theta = \frac{t}{\tau} \quad \text{and} \quad z = \frac{ut + x}{L} \tag{2.2}
\]
\[
\frac{dC}{d\theta} = \frac{D}{\bar{u}L} \frac{d^2C}{dz^2} - \frac{dC}{dz} \tag{2.3}
\]

These studies predict the spreading of a tracer in a fluid system as a function of a dispersion
coefficient, \( D \), which is a function of diffusion, \( D \), mean fluid velocity, \( \bar{u} \), and tube diameter, \( d \);
(equation 2.4)\textsuperscript{133}. While the concept of residence time distributions is broad, the dispersion
model is primarily applicable to flow through tubes or channels.

\[
D = D + \frac{\bar{u}^2 d^2}{192D} \tag{2.4}
\]
Two common techniques for performing RTD analysis of a flow system involve either injecting a pulse of tracer into a flow system or creating a step change in concentration. For a pulse injection, a tracer is injected into a carrier stream, and the response of the tracer is monitored after the reactor. Step change experiments operate by instantaneously switching the inlet feed concentration of a tracer and monitoring the dynamics until steady state has been achieved (Figure 2.1). For systems with significant dead volume between the reactor and tracers, measurements of the tracer form and deconvolution are necessary to assess the residence time distribution of just the reactor.

![Figure 2.1 - Pulse injections (left) and step change (right) experiments for performing residence time distribution experiments. The blue line represents the change to inlet conditions, and the red line represents the system response.](image)

The mean residence time, $\tau$, and variance, $\sigma^2$, for tubular reactors treated using the dispersion model are linked to the first and second moments to the solution of equation 2.3, respectively. For a hypothetical pulse injection, the mean residence time appears in equation 2.5, and the variance appears in equation 2.6.
\[ \tau = \frac{\int_0^\infty tC(t)\,dt}{\int_0^\infty C(t)\,dt} \quad (2.5) \]

\[ \sigma^2 = \frac{\int_0^\infty t^2C(t)\,dt}{\int_0^\infty C(t)\,dt} - \tau^2 \quad (2.6) \]

While some conflicting definitions exist in the literature about the definition of the Bodenstein number \( (Bo) \), we have chosen to define \( Bo \) as the ratio of convection to dispersion (equation 2.7) and the Peclet \( (Pe) \) number as the ratio of convection to diffusion (equation 2.8).

\[ Bo = \frac{\bar{u}L}{D} \quad (2.7) \]

\[ Pe = \frac{\bar{u}L}{D} \quad (2.8) \]

For systems where the Bodenstein number is greater than 100, spreading of an idealized pulse injection may be represented by a Gaussian approximation (equation 2.9). As spreading of the tracer occurs about the mean, the non-dimensional time \( \theta \) is the ratio of real time, \( t \), normalized to the bulk fluid residence time (equation 2.10). Furthermore, the variance spreads inversely to the Bodenstein number (equation 2.10)\(^{134}\).

\[ C(\theta) = \sqrt{\frac{Bo}{4\pi\theta}} \exp \left[ -\frac{Bo}{4} (1-\theta)^2 \right] \quad (2.9) \]

\[ \theta = \frac{t}{\tau} \quad (2.10) \]

\[ \sigma^2 = \frac{2}{Bo} \quad (2.11) \]

Normalization of the dimensional concentration \( C \) by total tracer quantity results in a convenient comparison between different reactor configurations and tracer systems (equation 2.12). This equation can also be readily written in non-dimensional time, \( \theta \), as well. These
curves are frequently referred to as either $E$ curves for pulse injection experiments or $F$ curves for step change experiments\textsuperscript{24}. $E$ and $F$ curves are interchangeable by integration or differentiation, respectively (equation 2.13). The Bodenstein number can also be simply calculated based on the maximum peak height of the $E(\theta)$ curve (equation 2.14)\textsuperscript{24}.

$$E(t) = \frac{C(t)}{\int_0^\infty C(t)dt} \quad \text{or} \quad E(\theta) = \frac{C(\theta)}{\int_0^\infty C(\theta)d\theta}$$

(2.12)

$$E(\theta) = \frac{d}{d\theta} (F(\theta))$$

(2.13)

$$\max \{E(\theta)\} = \frac{B_0}{\sqrt{4\pi}}$$

(2.14)

For systems where the Bodenstein number is less than 100, a dependence on the boundary conditions exists for the form of the mathematical approximations. Two types of boundary conditions are frequently used: 1) closed-closed, and 2) open-open. Closed-closed assume that plug flow (e.g. no velocity profile) exists outside of the region being modeled. Open-open boundary conditions assume a pre-existing fully formed velocity profile exists upon entering and exiting the modeled zone and are easier to model mathematically.\textsuperscript{130} The entrance length to achieve fully developed flow can be approximated by equation 2.15.\textsuperscript{133, 135} For a typical Reynolds number of 0.1-100 and channel width of 500 micron, this entrance length corresponds to 0.5-5.5 mm. Thus, open-open boundary conditions are adequate for microfluidic devices, which typically have lengths significantly longer than the hydraulic diameter.

$$\frac{L_{\text{entrance}}}{d_i} = 1 + 0.1 Re$$

(2.15)

Near Gaussian forms can still be used for these smaller Bodenstein number systems (equation 2.16), though a second order expansion is necessary to calculate the variance (equation 2.17).
 Thus for a pulse injection from an experimental system, the Bodenstein number, and hence system dispersion coefficient can be back calculated by either fitting the response curve to a Gaussian form or from calculating the variance of a system. The latter is preferable due to the ease of calculation.

Packed beds display an identical form for $E$ and $F$ curves at long bed lengths. Important parameters for estimating dispersion in packed beds include the bed length, $L_B$, and particle size diameter, $d_p$. The pulse response for a packed bed is given by equation 2.18. The radial Bodenstein number used in this form uses the particle diameter in place of the channel diameter or reactor length (equation 2.18)\textsuperscript{136}. Substitution of equation 2.18 into 2.17 reveals dispersion is dominated by the system Bodenstein number. The advantage of the form of equation 2.17 is that several easily measured parameters are incorporated into the model.

\begin{equation}
E(\theta) = \frac{L_B}{d_p} \frac{Bo_R}{4\pi \theta} \exp \left[ -\frac{L_B}{d_p} \frac{Bo_R}{4\theta} (1-\theta)^2 \right] \tag{2.17}
\end{equation}

\begin{equation}
Bo_R = \frac{\bar{u}d_p}{D} \tag{2.18}
\end{equation}

Deconvolution may be readily performed by inverse fourier transforms of the inlet change before entering the reactor and after exiting the reactor (equation 2.19)\textsuperscript{137,138}.

\begin{equation}
E(\theta)_{\text{deconvoluted}} = \text{FFT}^{-1} \left\{ \frac{\text{FFT} \left( E(\theta)_{\text{end}} \right)}{\text{FFT} \left( E(\theta)_{\text{in}} \right)} \right\} \tag{2.19}
\end{equation}

### 2.3 Inline UV-Vis spectroscopy setup

The inline system used for these experiments was comprised of several components (Figure 2.2). The basic components were 1) a pump for supplying fluid, 2) tubing to connect the various
components, 3) a 2-position 6-port valve, 4) a light source, 5) a flow cell, 6) a detector, and 7) software to record the results. The total current cost to replicate the system would be \( \sim $7000 \).

**Figure 2.2 – Schematic of inline UV-Vis platform for performing RTD experiments.**

Harvard Apparatus PhD 2000 syringe pumps were typically used to effect flow; however, other reasonable pumps could be substituted with little effect on the results. Glass syringes (SGE, 5 mL) were used to reduce oscillations in flow rate due to compliance in the syringe piston.\(^{139}\) For both pulse injection and step change experiments, a 2-position 6-port valve (Idex Health and Science) was used. The valve had slightly different configurations for each technique as detailed in Figure 2.3 and Figure 2.4. Notably a simple 2-position 3-port valve would have been sufficient for step change experiments. Sample loops for pulse injections were 5 cm of 0.01” ID PTFE tubing (~2.5 \( \mu \)L). The tracer concentration was readily changed to maintain a good signal to noise ratio. Connections between the reactor and tubing were made with 0.01” tubing when possible to reduce the dead volume between the valving, reactor, and flow cell. For single liquid phase or liquid-liquid multi-phase experiments, back pressure was applied using a spring loaded back pressure regulator (5 – 20 psig, Idex Health and Science) to reduce the possibility of degassing from affecting results.
Figure 2.3 – Pulse injection RTD experimental setup. Loading sample loop (left) and after an injection (right).

Figure 2.4 – Step change RTD experimental setup. Blank carrier solvent (left) and carrier solvent containing tracer (right) flowing through the reactor.

Two types of flow cells were used in these experiments: a commercial “Z” flow cell was sufficient for single phase liquid experiments (FIA-1000-Z, Ocean Optics,); however, the long path length (10 mm) relative to a typical slug length (3-5 mm) resulted in significant noise during liquid-liquid or gas-liquid experiments due to refraction at the interface of the two phases. Furthermore, the wetted parts at the optical connection were silica, which prevented alkaline solutions from being used and limited pressures to only 25 psi. For liquid-liquid applications, the Z cell had the further disadvantage of being made of stainless steel, which is significantly more hydrophilic compared to the PTFE tubing typically used for other applications. The change in surface wetting could impact slug flow behavior during measurements.
A "cross" flow cell was designed and fabricated that was found to have superior performance for multi-phase experiments and also worked well for single phase liquid experiments (Figure 2.5). The main cell was fabricated by First Cut (www.firstcut.com); however, all holes were drilled and ports were tapped at the MIT student machine shop. The cross cell did not have wetted parts; the orifice was sized to snugly fit 1/16" PTFE tubing, and the "outlets" comprised 1/4-28 fittings. In this manner, tubing could be secured without use of epoxy. Connections to the fiber optic cables were made using SMA adapters (1/4-36). The optical transparency of the PTFE tubing was sufficient for measurements to be made. Each flow cell had space for two connections to potentially enable multiple connections to be made as well as reduce the chance of misalignment while drilling the optical and fluidic through holes (Figure 2.6).
A combination deuterium-halogen light source was used (DH-2000, Ocean Optics), which provided sufficient light for measurements to be made in the 260-700 nm range. Typically only a fraction of this range was used during experiments. A variety of fiber optic cables were used with little to no effect on results; however, as measurements were frequently made below 300 nm, all cables used were solarization resistant. A spectrometer (USB2000, Ocean Optics) was used to capture data. This spectrometer could be readily hooked up to any modern computer using a USB connector. Commercial software was used to capture data (SpectraSuite, OceanOptics). This software was Java-based and would occasionally freeze if other applications using Java were running at the same time. The software stored results as a 3-column text file with headers of real time, experimental time, and data. A digital timer was used to record relative times; thus, experimental times were used for data analysis.

2.4 Experimental protocol

Correct operation of the software was as important as correctly configuring the experimental setup. Before an experiment was started, but after all connection were made to achieve the
desired configuration, both lamps on the light source were turned on and were allowed to warm up for 20 minutes. Immobilization of the flow cell using a clamp and fiber optic cables were necessary to prevent disturbances to the signal. The shutter was kept closed during this time, and a “dark spectrum” was taken.

While the lamp was warming up, the carrier solvent was flowed through the system at the desired flow rate. A typical flow rate investigated was 10-100 µL/min, though flow rates outside of this range were possible. These flow rates allowed reasonable throughputs of experiments. Typically reagent grade methanol was used as the carrier solvent, with toluene (0.1 – 10 vol%) as a typical tracer for both pulse and step experiments. The tracer solvent and carrier solvent were always identical. Other potential tracer and carrier combinations include sodium benzoate in water or acetone in hexane.

Once the lamp was completely warmed and the carrier solvent had achieved a steady state, a blank reference spectrum was recorded. This step was necessary for absorbance measurements but was not necessary for intensity measurements. Note that changes to the flow rate would sometimes affect baseline measurements of the carrier solvent. This effect was more pronounced using the Z flow cell due to changes in the ratio of residence time within the cell to sampling time.

Data was recorded as a “strip chart,” which monitored either a single wavelength or range of wavelengths as a function of time. Wavelength, scanning frequency, and number of scans to average could all be changed. As the spectrometer used could only discern between intensities in the range of 250-4000 counts, the scanning frequency was adjusted to ensure the carrier solvent was within this range. While the number of scans to average reduced the signal to noise ratio of the data and reduced the file size, this option was frequently left at 1 (e.g. not used), as the
offline data analysis algorithm smoothed the data. For the toluene in methanol system, wavelengths from 260-285 nm were typically monitored. RTD measurements were initially performed using absorbance but were later performed by monitoring intensity. Intensity, I, and absorbance, A, are related through the Beer’s law (equation 2.20).

\[ A = \ln \left( \frac{I}{I_0} \right) \]  

(2.20)

Pulse injections and step change experiments were performed by manually activating the 6-port 2-position valve and recording the experimental time. The external and software experimental times were manually synchronized by clicking the “reset” button at the same time the timer was started. A time of one minute was allowed to elapse before the first injection to allow recording of the baseline. Experiments were terminated when the baseline had visually returned to the baseline for pulse injections or appeared to completely flatten for step changes. All experiments were performed in triplicate.

For pulse injections, the tracer loop was normally open to the carrier solvent. During an injection, the tracer loop was quickly closed, loaded with tracer, and reopened. This technique both minimized pressure disturbances to the system and ensured the tracer injection volume was consistent between experiments. The pulsed volume was kept as small as possible relative to the reactor volume; however, a minimum injection volume of ~2.5 µL was achievable. For reactor volumes < 100 µL, a smaller tracer injection volume could have been desirable. Pulse injections in biphasic RTD measurements were introduced into a single phase before the two phases contacted.

Step change experiments had two advantages relative to pulse injections; only a single valve actuation was necessary; comparison of injection volume to reactor volume was required. This technique assumed ideal flow switching, which may have been problematic if the cartridge back
pressure regulators on each line were not identical. Furthermore, differentiation was necessary to convert experimental data to a pulse injection for analysis. Thus, pulse injections remain the preferable option.

Tubing connections were made with 0.01” (250 micron) ID tubing when possible and was kept as short as possible to minimize dead volume. Tubing through the cross flow cell was typically 0.02” (500 micron) ID.

2.5 Data analysis algorithms

After saving data obtained using the SpectraSuite software, custom MATLAB software was used to filter and analyze the data. Three different MATLAB programs were used for data analysis and plotting, though a separate program was used for single phase vs. multi phase systems. Deconvolution could be performed manually if necessary using MATLAB to perform the fast fourier transforms. The full programs appear in Appendix A. A brief description of each program follows. MATLAB program titles are denoted in bold with a .m suffix.

1. **RTDprog.m** – main program for performing data analysis for single phase liquid experiments. **RTDprog.m** is used for single-phase systems, whereas **RTDcross.m** has different filtering algorithms and should be used for multi-phase systems. **RTDprog.m** requires four inputs: 1) *fname*: the .txt file name for analysis, 2) *n_inj*: the number of experiments to be analyzed, 3) *n_point*: number of data points used to smooth the data, and 4) *ax_vec*: array indicating scale to plot outputs. After opening the .txt file, redundant data points are removed to compact the file size. Injection time points are read from program 3, **gen_a.m**. The entire data set is plotted both before and after data smoothing to assist in visual identification of specific plots. Each injection within the file is normalized so that the baseline concentration is set to
zero; furthermore, a linear transformation between the initial and final time point is made to account for signal drift. The calculations described in equations 3.5 through 3.11 are performed, and both a figure and text file containing columns of time, concentration, $\theta$, $E(t)$, $E(\theta)$, $\sigma^2(t)$, and the skew are generated. This process is repeated for each injection within the data file, and then all injections are overlayed on a single figure using program 4, RTDplotter.m.

2. **RTDcross.m** – main program for performing data analysis for biphasic gas-liquid or liquid-liquid experiments. This program functions identically to RTDprog.m except that two additional data filters are employed. The first filter acts as a low pass filter by removing data that has changed too drastically between points, as these large changes typically correspond to a phase change. The second filter removes data from the phase that doesn’t contain the tracer. Thus RTDcross.m has a total of 6 inputs, of which the first four are identical to those described in RTDprog.m. The last two inputs are 5) noise: the magnitude of the differentiation below which data remains in the experimental set, and 6) $B_{vec}$: the range of intensities or absorbances that correspond to the phase not being analyzed. Other calculations and functionality between RTDprog.m and RTDcross.m were identical.

3. **gen_A.m** – shell program for storing injection times and flow rates. Data for each data set is entered as a matrix with $n_{inj}$ rows and columns of 1) start time, 2) stop time, and 3) volumetric flow rate in $\mu$L/min. Matrices with more than $n_{inj}$ rows could be entered; however, only the first $n_{inj}$ points called by RTDprog.m or RTDcross.m are analyzed.
4. **RTDplotter.m** — program for overlaying multiple injections onto a single plot that is called within **RTDprog.m**. This program can also be called independently to plot multiple experiments against each other and read the reduced .txt injection files. Both $C(t)$ vs. $t$ and $E(\theta)$ vs. $\theta$ plots are generated. **RTDplotter.m** consists of three inputs:

1) *fname* — file name without .txt extension
2) *n_inj* — number of injections to overlay,
and 3) *n_exp* — number of experiments to analyze. If *n_exp* is larger than 1, subsequent file name and number of injections for each data file beyond the first must be manually entered.

### 2.6 Single phase liquid results

Initial characterization experiments were performed on a 140 µL 400x400 µm² square channel microreactor using toluene in methanol at a liquid flow rate of 10 µL/min. The raw absorbance data at 265 nm at data collection frequencies of 6 Hz provided reasonably clean data, though smoothing the results by averaging every 30 data points (5 seconds) results in significantly higher signal to noise ratio. The experimental results appear in Figure 2.7. The mean residence time in the system including dead volume was 1143 ± 11 s. The maximum height of the $E(\theta)$ vs $\theta$ curve was 3.93, which corresponds to a Bodenstein number of 194. With a path length of 0.88 m and a mean fluid velocity, $\bar{u}$, of 1 mm/s, the dispersion coefficient in the microreactor is thus $4.7 \times 10^{-6}$ m²/s. The calculated diffusion coefficient using equation 2.4, 0.0028 mm²/s, was almost identical to the literature value of 0.00276 mm²/s.
Figure 2.7 – Single phase RTD measurements. Top left: Raw data. Top right: Post processing of raw data. Bottom left: Three injections in $C(t)$ vs $t$. Left: Three injections in $E(\Theta)$ vs $\Theta$.

The system was also applied to characterize the void fraction in porous media by measuring the volume change of the reactor. The RTD of a packed bed reactor both before and after loading with porous particles was measured using toluene in methanol tracers at flow rates of 50 $\mu$L/min. The mean residence time of the reactor including dead volume before loading was 363 ± 2 s. After filling the reactor with fluorous silica gel beads ($d_p \sim$ 70 micron), the mean residence time was 316 ± 2 s. The difference in volumes between the packed bed and empty reactor was 34 $\mu$L, which implies an overall void fraction of 74%. As the internal porosity of the gel had separately been measured to be 54%, the packing efficiency was estimated to be 48%. Details of the reactor design and measurements of internal porosity appear in chapter 5 of this thesis. Notably the microreactor showed significantly reduced dispersion when packed compared to unpacked (Figure 2.8).
While the platform was used for a number of other measurements, these two examples demonstrate the utility and reproducibility of the platform. A third example of the Mettler Toledo FTIR flow cell follows. This flow cell has a nominal internal volume of ~51 µL as reported by the vendor; however, the internal structure was thought to resemble a T, which could induce recirculation eddies or be problematic for multi-phase flows should a bubble become trapped. Issues with data reproducibility using gas-liquid multi-phase systems had previously been reported. Thus, the single phase RTD was measured at flow rates of 100 µL/min with the flow cell and without the flow cell were measured. As intensity instead of absorbance was monitored for this particular experiment, a negative peak was observed. This type of peak had no effect on the calculations (Figure 2.9). While significant peak broadening was observed, the \( E(\theta) \) curves were fairly similar, though the peak without the flow cell had shifted right. The shift indicates some degree of recirculation eddies are present within the cell.
Figure 2.9 – Use of RTD platform to measure internal volume of an inline FTIR flow cell. Left: Intensity vs. time. Right: \( E(\theta) \) vs \( \theta \).

The mean residence time without the flow cell was \( 25.2 \pm 0.7 \) s, and the mean residence time with the flow cell was \( 55.9 \pm 0.7 \) s. The total observed volume of the flow cell \( 51.1 \pm 1.2 \) \( \mu \)L, which corresponds very closely with the volume the manufacturer claims.

2.7 Multi-phase liquid-liquid and gas-liquid results

Efforts were made to characterize liquid-liquid multi-phase flows using the inline UV-vis platform. Initial experiments with water-hexane using the Z flow cell appear in Figure 2.10. The large spikes are phase changes at the menisci and likely occur when a slug is leaving the flow cell. Analysis of pulse injection data was problematic, as absorbance measurements of the tracer (toluene in hexane) overlapped with the water phase. While the data filtration algorithms previously described were applied and were able to capture most of the data, a significant fraction of the data points recorded were removed.

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\( ^{\dagger} \) Experimental work in this section was performed in collaboration with Dr. Ryan Hartman, Dr. Chris D. Smith, and Dr. Simon Kuhn, who were postdoctoral researchers in the Jensen group. Themes from this section appear in *Langmuir* 2011, 27, 6519–6527.
These experiments were repeated using the cross flow and were used to investigate the dispersion and wetting characteristics of native oxide and PTFE coated silicon microreactors (Figure 2.11).\(^7^6\) As the absorbance of the tracer overlapped water in the previous experiments, the tracer was switched to sodium benzoate in water. Furthermore, hexane was replaced with toluene as the organic phase. The concentration of the sodium benzoate tracer was reduced such that the pulse injections of the tracer did not overlap the signal from the organic phase.
Figure 2.11 – Wetting characteristics of native oxide (left) and PTFE coated (right) microreactors for liquid-liquid multi-phase flows. The water segments are dyed using fluorescein.

Use of the cross flow cell resulted in significantly reduced noise in the data and allowed for accurate measurements of the dispersion coefficients. Two flow rates, 10 μL/min and 25 μL/min, were investigated at equal volumetric flow rates of each phase. Notably the large spikes at either end of a slug were eliminated (Figure 2.12).

Figure 2.12 – Clean multiphase liquid-liquid RTDs obtained using a cross flow cell.

The use of PTFE coated microreactors resulted in reduced communication between aqueous slugs, as evidenced by the reduced dispersion coefficient. Given that the aqueous phase should be completely encapsulated by the organic phase in a PTFE coated microreactor, the dispersion coefficient should be reduced even beyond what was observed. To verify that no communication occurred between slugs, laser induced fluorescence measurements using Rhodamine 6G of a
single slug were monitored throughout the chip. For the native oxide microreactors, the fluorescence decreased at the outlet of the reactor, which indicated diffusive losses of the excited material through the corners of the slugs. Conversely, the PTFE coated microreactor showed nearly identical intensities at the inlet and outlet. As the volume of a single slug (8 mm long, ~1 μL) is lower than the tracer injection volume (2.5 μL), and the injection occurs before the two phases contact, breakup of the injection over multiple slugs and spreading prior to injection is largely responsible for the observed dispersion \(^{142}\). The results and extrapolated dispersion coefficients appear in Table 2.1.

<table>
<thead>
<tr>
<th></th>
<th>(Q) (μL/min)</th>
<th>(\tau) (s)</th>
<th>(D) (mm(^2)/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>silicon</td>
<td>10</td>
<td>1725±12</td>
<td>2.62</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>668±2</td>
<td>6.79</td>
</tr>
<tr>
<td>PTFE</td>
<td>10</td>
<td>1774±25</td>
<td>1.87</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>693±8</td>
<td>4.91</td>
</tr>
</tbody>
</table>

Gas-liquid multi-phase flows provide excellent mass transfer at the microscale \(^{102, 143}\) and previous work on characterizing gas-liquid residence time RTDs has shown reduced dispersion relative to single phase flows \(^{137, 142, 144}\). This platform was used to investigate gas-liquid multi-phase RTDs through both silicon microreactors and packed bed. Methanol:nitrogen in a ~ 1:1 volumetric flow rate at a back pressure of 10 bar were passed through both a silicon microreactor (220 μL) and a packed bed of stainless steel beads (660 μL). The volumetric flow rate of gas was controlled using a calibrated mass flow controller. Integration of absorbance across the range 250 – 300 nm was recorded. Toluene (10 vol%) in methanol was used as the tracer. Characterization of a union connecting two pieces of tubing revealed some hold up, as demonstrated by the elution of slugs containing tracer following the bulk of the tracer over
several experiments (Figure 2.13). Reproducibility of the injections was quite good, as the mean residence time for 5 injections was $109.8\pm1.9$ s.

Figure 2.13 – Multiphase GL RTD of a union using the cross flow cell. Top left: Raw pulse injection data before processing. Top right: Zoom in of slug flow. Bottom left: Overlay of 5 injections post processing. Bottom right: Zoom in of baseline of 5 injections post processing.

RTD curves both for the silicon microreactor and packed bed microreactor were obtained (Figure 2.14). The microreactor $E(\theta)$ curve had a maximum height of 7.4, which corresponds to a Bodenstein number of 694 and dispersion coefficient of $5.1 \text{ mm}^2/\text{s}$ ($L = 880 \text{ mm}$, $\bar{u} = 4 \text{ mm/s}$). The packed bed $E(\theta)$ curve had a maximum height of 5.6, which corresponds to a Bodenstein number of 398 and dispersion coefficient of $0.88 \text{ mm}^2/\text{s}$ ($L = 100 \text{ mm}$, $\bar{u} = 0.35 \text{ mm/s}$). The lower dispersion coefficient in the packed bed is largely due to the reduced velocity and wider channel.
2.8 Conclusions

A general modular platform for performing residence time distribution measurements has been developed. The experimental methodology and data analysis algorithms have been standardized such that the system can be readily integrated into a number of different reactor configurations and can be applied both to single phase and multi-phase experiments.

The system has been applied to a number of different platforms. Proof-of-concept experiments with single phase liquid experiments demonstrated robust operation with excellent reproducibility. The system was also used to determine the internal porosity of fluorous silica gel in a packed bed microreactor. The internal volume of a commercial FTIR flow cell was verified and some internal recirculation was observed.

Reduced communication between aqueous slugs in liquid-liquid biphasic systems by converting a hydrophilic surface to a PTFE surface was demonstrated. The liquid phase residence time distribution of a gas-liquid system through a packed bed was measured. In all cases, extraction of dispersion coefficients was achieved.

Comparisons of the RTD curves for gas-liquid multi-phase flows through both a packed bed and silicon microreactor were achieved. The packed bed was found to display slightly worse
dispersion characteristics relative to the silicon microreactor; however, both systems showed significantly less dispersion compared to single liquid phase flow.

The current platform has several advantages relative to other techniques previously used to measure RTDs. These advantages include the ability to measure both single and multiphase systems easily using the same experimental setup and the ability to incorporate the platform into a number of different reactor configurations. The main disadvantage of this platform relative to others reported is the need to perform two injections to resolve the residence time of a single reactor. This issue could be easily circumvented in the future by addition of a second flow cell into the setup.
3. Motivation

A number of approaches to optimizing chemical processes exist and can be broadly grouped into empirical or model based approaches. One classic empirical approach is the design of experiment (DOE)\(^{145}\), which examines several parameters of interest over a range of conditions, and then uses statistical analysis to determine which parameters are the most important. While this approach has the advantage of requiring little pre-existing knowledge, the results obtained using this technique may not impart fundamental knowledge, which can limit application of the results either to different systems or to the same system at a different scale. Furthermore, the number of experiments scales exponentially with the number of parameters under investigation.

Model based approaches for chemical synthesis may involve analysis of reaction kinetics, mass transfer, heat transfer, and fluid flow profiles within a reactor. Fortunately, isothermal operation in microreactors has proven to be a reasonable assumption\(^{58, 82, 92, 146}\), and for single phase liquid reactions, initial mixing and fluid flow profiles through a tube are well understood. Kinetic analysis can thus be the focus for many cases, which entails determining the rate model, pre-exponential factor, and activation energy of the rate constant. Complete kinetic knowledge of a system transforms a process optimization problem into a mathematical problem that can be more readily solved. Classical techniques for performing kinetic analysis can require a large number of experiments; analysis of a series-parallel epoxide aminolysis reaction required 105 experiments\(^{82}\). Alternatively, accurate determination of a kinetic model can be difficult if the mechanism is poorly understood. For example, kinetic analysis of the production of sodium

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\(^{†}\) Experimental work in this chapter was done in collaboration with Dr. Bo Shen, who at the time was a post-doctoral researcher in Prof. Tim Jamison’s lab in the Department of Chemistry at MIT.
nitrotetrazole revealed the preexponential factor was strongly affected by both the pH and ionic strength of the system\textsuperscript{59}.

A technology receiving increasing attention involves controlling experiment selection in an automated fashion with in-line analysis. Use of Neader Meld simplex optimization algorithm of a Heck reaction\textsuperscript{91}, activity screening of acid catalysts\textsuperscript{87}, library development\textsuperscript{89}, and kinetic analysis of a Diels-Alder reaction\textsuperscript{92} have all been demonstrated in an automated fashion. As this technology is fairly new, platform development can require a significant investment in both capital and time.

Consideration of these techniques reveals process optimization requires either a large number of experiments or a large capital investment. To fully understand a system, some combination of the above techniques will likely be required; however, the ability to make rapid adjustments to a flow system based on preliminary data would provide a valuable intermediate step in process optimization. This chapter attempts to elucidate when mixing or dispersion are important based on a system Fourier number and an estimate of the rate model.

### 3.2 Reactor model selection

Selection of an appropriate reactor model is an important choice when modeling a chemical system. In an ideal batch reactor, the system is assumed to be well mixed and concentration changes as a function of time (equation 3.1). Similarly, the simplest reactor model for fluid flowing through a channel is the “plug flow” model, where the radial concentration profile is assumed to be uniform and axial concentration profiles change as a function of distance. When distance is converted into residence time by assuming an average velocity (equation 3.2), and there are no volume changes during the reaction, the two models have an identical form. The
plug flow reactor model thus provides an easy analogy to compare flow chemistry with batch chemistry.

\[
\frac{dA}{dt} = R_A \tag{3.1}
\]

\[
\frac{dA}{d\tau} = R_A \tag{3.2}
\]

Most small scale liquid phase flow systems have Reynolds numbers significantly less than 2000, which means these systems exhibit laminar flow and have a parabolic flow profile (equation 3.3). Fluid at the center of the channel spends half as much time in the reactor compared to fluid at the walls, yet microreactors are frequently described by plug flow or near plug flow behavior. How does one reconcile plug flow behavior with a parabolic flow profile?

\[
u(r) = u_{\text{max}} \left(1 - \left(\frac{2r}{d_c}\right)^2\right) \tag{3.3}
\]

Plug flow behavior can only be achieved if radial diffusion across a channel is much faster than convective mass transfer down the channel and must be a function of reactor diameter. The dispersion model, derived by Taylor and Aris in the early 1950s\textsuperscript{131, 132}, provides a general framework to estimate when a plug flow model is appropriate, as well as how to account for systems that deviate from plug flow. Accounting for dispersion is important when analyzing data obtained from a flow system as well as when deciding how to scale results. While most microreactors will use a plug flow with dispersion model\textsuperscript{147, 148}, a laminar flow reactor (LFR) model may be more appropriate for extremely fast reactions in short tubes.

An important condition necessary to apply the plug flow model with dispersion is that the tube length is sufficiently long such that fully developed flow is achieved\textsuperscript{134}. Details of LFR models are available in standard textbooks\textsuperscript{24, 149}. Froment and Bischoff give guidelines for when to use a plug flow model with dispersion (equation 3.4)\textsuperscript{134}, though rewriting the equation in
terms of residence time results in a Fourier number ($Fo$), which describes the ratio of residence
time to diffusion time (equation 3.5), results in a more convenient form (equation 3.6).

$$\frac{L}{d_t} > 0.04 \frac{\bar{u}d_t}{D}$$  \hspace{1cm} (3.4)

$$Fo = \frac{\text{residence time}}{\text{transverse diffusion time}} = \frac{4D\tau}{d_t^2}$$ \hspace{1cm} (3.5)

$$Fo > 0.16$$  \hspace{1cm} (3.6)

The Taylor dispersion coefficient, $D$, incorporates the effect of both diffusion, $D$, and
convection$^{24,131}$. Convective mass transfer dominates diffusion effects in most small scale flow
systems, which enables the diffusive portion of the Taylor dispersion coefficient to be neglected
(equation 3.7). The parameter $\beta$ depends on channel geometry and is $48$ for circular tubes and
$\sim 30$ for square channels$^{150}$.

$$D = D + \frac{\bar{u}^2d_t^2}{4\beta D} = \frac{\bar{u}^2d_t^2}{4\beta D}$$  \hspace{1cm} (3.7)

The requirement for ignoring the diffusion component in equation 3.7 is maintaining the
Peclet number based on tube diameter, $Pe_d$, above $50$ (equation 3.8). Calculation of $Pe_d$ reveals
the assumption to be valid only for flow systems with extremely low flow rates (Figure 3.1).
The parameter $\alpha$ depends on channel geometry and is $\pi/4$ for circular tubes and $1$ for square
channels.

$$Pe_d = \frac{\bar{u}d_t}{D} = \frac{Q}{\alpha d_t D} > 50$$  \hspace{1cm} (3.8)
Figure 3.1 – Tie lines for $Pe_d=50$ in both square channels and circular tubes. A diffusion coefficient of $10^{-9}$ m$^2$/s was assumed.

### 3.3 Dispersion effects in flow systems

Maintaining the definitions used in chapter 2, the Bodenstein ($Bo$) number represents the ratio of convection to dispersion and can be used to estimate deviations from plug flow (equation 3.9). Combining equations 3.7 and 3.9 results in a simple estimate on the magnitude of dispersion effects using the system Fourier number and channel geometry (equation 3.10).

\[
Bo = \frac{\bar{u}L}{D} \tag{3.9}
\]

\[
Bo = \frac{4\beta D\tau}{d_i^2} = Fo\beta \tag{3.10}
\]

While the exact effects of dispersion on chemical conversion depend on the kinetic model, systems with $Bo > 100$ have small deviations from plug flow, and systems with $Bo < 100$ display large deviations from plug flow\textsuperscript{24}. Systems with $Bo > 1000$ may be approximated as having plug flow behavior, as >95% of the fluid has a residence time within 8% of the bulk fluid residence time. These guidelines are plotted as tie lines in Figure 3.2. Notably, dispersive effects are more pronounced in square channels compared to circular tubes due to increased fluidic holdup in the corners\textsuperscript{150}. Both 500 micron diameter capillary tubes and 400 micron square channel reactors show plug flow characteristics at residence times > 20 minutes. Large deviations from
plug flow are expected for reactions with residence times less than 120 seconds in capillary reactors and 150 seconds in 400 micron square channels.

Figure 3.2 – Magnitude of dispersion effects in circular tubes (top) and square channels (bottom).
The largest source of error likely comes from correctly estimating the diffusion coefficient. While a typical liquid phase diffusion coefficient is \(10^{-9} \text{ m}^2/\text{s}\), gas-phase systems have diffusion coefficients on the order of \(10^{-5} \text{ m}^2/\text{s}\), protons in aqueous solutions are closer to \(3 \times 10^{-8} \text{ m}^2/\text{s}\), and large macromolecules may be less than \(10^{-10} \text{ m}^2/\text{s}\)^1. Several correlations exist to predict diffusion coefficients when more accurate estimates are required\(^{152,153}\). As the diffusion coefficient approaches zero, dispersion effects become more pronounced and achieving plug flow becomes more difficult. Representative plots appear in Figure 3.3.

\[ D = 10^{-9} \text{ m}^2/\text{s} \]

\[ D = 10^{-9} \text{ m}^2/\text{s} \]

\[ D = 10^{-10} \text{ m}^2/\text{s} \]

**Figure 3.3 – Effect of diffusion coefficient on dispersion phase diagram.**

The current analysis assumes a straight tube and does not take into account methods of reducing dispersion. Periodic static mixers or a second phase can be introduced to disrupt the
laminar flow profile. Alternatively, use of coiled tubes with Dean numbers greater than \(-10\) can reduce dispersion effects due to outward radial flow (equation 3.11)\(^{154}\).

\[
De = \frac{\rho v d}{\mu}\left(\frac{d}{d_{\text{curve}}}ight)^{1/2}
\]  
(3.11)

Furthermore, as the Fourier number has no velocity or length component, a technique for scale-up that has not achieved much attention in the literature is to linearly increase the reactor length and flow rate. In this manner, dispersion effects remain constant. This scale-up technique may be simpler than running several devices in parallel due to difficulties ensuring uniform flow distribution though has the obvious disadvantage of higher operating pressures. Figure 3.2 also provides an estimate of whether increasing tube diameter will result in significantly increased dispersion effects. For cases where these transitions result in moving from a region of plug flow or near plug flow to a region where significant dispersion effects are expected, incorporation of an appropriate residence time distribution model for simple kinetic models is possible to predict performance in a reactive flow system (equation 3.12)\(^{24,82,92}\).

\[
X_{\text{reactor}} = \int X_{\text{PFR}} E(t)\,dt
\]  
(3.12)

For more complex systems where analytical solutions to the reaction system do not exist, computational fluid dynamic simulations may assist in quantifying dispersion effects on reactor performance.

### 3.4 Analysis of mixing

The lack of turbulence and recirculation eddies in laminar flow reactors means that radial mixing is strictly due to diffusion. Fick's law is frequently used to describe mixing within microchemical systems (equation 3.13). This equation can be solved using a similarity method to give penetration depth as a function of time and diffusion coefficient. For rectangular channels
with equal flow rates, the penetration depth to achieve complete mixing is half of the channel width; for a tubular capillary, the penetration depth can be approximated as the channel radius. The solution to this problem for 99.5% mixing corresponds to the well known equation describing mixing time (equation 3.14)\(^{133}\).

\[
\frac{dA}{dt} = D \frac{d^2 A}{dx^2}
\]

(3.13)

\[
\tau_{mix} = \frac{d^2}{4D}
\]

(3.14)

Despite neglecting the impact of reaction, equation 3.14 is frequently cited as a characteristic mixing time. For 400 micron channels, this mixing time corresponds to 40 seconds; for 1 mm, the necessary mixing time is 250 seconds.

For reactive systems, approximations using Fick’s law can lead to improper conclusions regarding a system. A more accurate analysis relies on the Damköhler number (\(Da\)), a dimensionless number describing the relative rates of reaction and mass transfer in a system (equation 3.15). \(Da > 1\) implies the reaction is faster than diffusion and the existence of concentration gradients within a system. Analysis of the system Damköhler number thus provides an estimate of whether enhanced mixing is required.

\[
Da = \frac{\text{rate of reaction}}{\text{rate of mixing}}
\]

(3.15)

The exact form of the Damköhler number depends on the kinetic model, and for bimolecular reactions with different molar feed rates, two separate Damköhler numbers are required to model the system. As an example, consider the reaction-diffusion equation (equation 3.16-18) for the second order system \(A + B \rightarrow C\). The two Damköhler numbers for the system are given by equations 3.19-20.

\[
\frac{dN}{dt} = D \frac{d^2 N}{dx^2} - R_N, N = A, B, C
\]

(3.16)
\[ R_A = R_B = -k_{AB} \]  
\[ R_C = k_{AB} \]  
\[ Da_A = \frac{k_B d_i^2}{4D} \]  
\[ Da_B = \frac{k_A d_i^2}{4D} \]

The above system was modeled as two parallel stagnant films with step changes in concentration using COMSOL 3.2. Velocity profile effects were neglected, as these effects determine the reactor model and should have minimal impact on mixing behavior at typical microfluidic mixing velocities for residence times on the order of minutes. Only when the Reynolds number exceeds \(~100\) do engulfment effects begin to influence mixing, which corresponds to a volumetric flow rate of \(~2.4\) mL/min of water through 500 \(\mu\)m ID tubing\textsuperscript{155,156}. The Damköhler number was readily changed by changing the rate constant while maintaining a constant geometry. The number of equivalents of \(B\) were also changed to examine cases where the Damköhler number was less than one for \(B\) and greater than one for \(A\). Cross sectional concentrations of \(A\) appear in Figure 3.4 for two cases: \(Da_A=Da_B=0.04\), and \(Da_A=Da_B=4\).

![Figure 3.4](image)

**Figure 3.4** – Concentration profiles of \(A\) for \(Da_A=Da_B=0.04\) (left) and \(Da_A=Da_B=4\) (right). Time has units of seconds.
In the former case, a nearly uniform concentration gradient (<10% difference) is achieved after 60 seconds, while only 2.6% conversion has been achieved. Conversely, in the latter case, the concentration of A still varies by 25% across the channel after 60 seconds, although 71% of A has reacted. The variations are worse at 40 seconds — 25% variation compared to 74% variation, respectively. Cross sectional concentrations of A and B for \( Da_A = Da_B = 0.4 \) and \( Da_A = 1.6 \) and \( Da_B = 0.4 \) appear in Figure 3.5.

![Figure 3.5 - Concentration profiles of A for \( Da_A = 0.4 \) (top left), \( Da_A = 1.6 \) (top right) and the concentration profiles for B for both cases (bottom left and bottom right). \( Da_B = 0.4 \) for both cases. Time has units of seconds.](image)

Notably, the plots of B look nearly identical except for the scale of the y-axis. Indeed, the relative concentration gradients are nearly the same for both cases. Conversely, the relative
concentration gradient for A are slightly worse when $Da_A=1.6$ compared to when $Da_A=0.4$. The results for all four cases are summarized in Table 3.1.

Table 3.1 – Comparison of conversions and species concentration gradients at 40 seconds and 60 seconds at different Damköhler numbers. Conversions are calculated by integrating across the entire channel.

<table>
<thead>
<tr>
<th>$Da_A$</th>
<th>$Da_B$</th>
<th>$t = 40 \text{s}$</th>
<th>$t = 60 \text{s}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$X_A$</td>
<td>$\frac{\max{A}}{\min{A}}$</td>
</tr>
<tr>
<td>0.04</td>
<td>0.04</td>
<td>1.6</td>
<td>1.25</td>
</tr>
<tr>
<td>0.4</td>
<td>0.4</td>
<td>14.2</td>
<td>1.29</td>
</tr>
<tr>
<td>1.6</td>
<td>0.4</td>
<td>45.7</td>
<td>1.43</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>60.2</td>
<td>1.74</td>
</tr>
</tbody>
</table>

For series-parallel reaction systems, such as where C can further react with A in the previous example, an estimate of whether increased byproduct formation is possible due to concentration gradients comes from plotting equation 3.21, which accounts for the increased presence of C relative to B (Figure 3.6).

$$byproduct\ potential = \frac{AC}{B}$$ (3.21)

As species A is required for C to react, the equation is scaled by the local concentration of A. For a well mixed system with equimolar feed rates, the byproduct potential would be uniform across a channel and would be equal to $C$. In the case of a $Da_A=4$, the byproduct potential due to concentration gradients was nearly 25 times greater than when $Da_A=0.04$. Increasing the number of equivalents of B did suppress byproduct potential, as expected.
Figure 3.6 – Enhanced byproduct potential due to the presence of concentration gradients. $D_{A,i} = 0.04$ (top left), $D_{A,i} = 4$ (top right), $D_{A,i} = 0.4$ (bottom left), $D_{A,i} = 1.6$ (bottom right). The axes of the top plots are not normalized to show the difference in behavior. The axes of the bottom plots are normalized to show that feeding additional equivalents of B does suppress byproduct formation even though the concentration profile of A is slightly less uniform. Time has units of seconds.

An estimate of the initial rate constant can be made by regressing the conversions obtained from integrating across the channel. Initial rate constants were calculated from best fit of conversion data when $X_A < 25\%$ by plotting time versus the left side of either equation 3.22 for equimolar feed rates or equation 3.23 when an excess of B was simulated (Figure 3.7). The parameter $M$ in equation 3.23 corresponds to the initial molar feed ratio of B to A. These equations come from the analytical solutions to the ODEs describing the system, and the slope in both cases corresponds to the apparent rate constant.

$$\frac{1}{A} - \frac{1}{A_0} = kt$$  \hspace{1cm} (3.22)
\[
\frac{1}{A_0 (M - 1)} \ln \left( \frac{M - X_A}{M - MX_A} \right) = kt, \quad M \neq 1
\]  

(3.23)

Figure 3.7 – Best fit of rate constants from COMSOL simulations using equation 4321 for equimolar feed rates (left) and equation 3.22 for nonequimolar feed rates (right).

Notably, the initial rate for both cases where \( Da > 1 \) had initial rates that were ~50% lower than the actual value, whereas the initial rate for the system with \( Da = 0.04 \) was within 2% of the correct value. These results are summarized in Table 3.2.

| \( Da \) | \( M \) | \( k_{\text{actual}} \) (s M\(^{-1}\)) | \( k_{\text{apparent}} \) (s M\(^{-1}\)) | Error (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.04</td>
<td>1</td>
<td>0.001</td>
<td>0.00098</td>
<td>2</td>
</tr>
<tr>
<td>0.4</td>
<td>1</td>
<td>0.01</td>
<td>0.0092</td>
<td>8</td>
</tr>
<tr>
<td>1.6</td>
<td>4</td>
<td>0.01</td>
<td>0.0055</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>0.1</td>
<td>0.049</td>
<td>51</td>
</tr>
</tbody>
</table>

The relative errors scaled to the predicted conversion show that initial behavior is much worse in both cases where \( Da > 1 \), which also appears when comparing analytical conversions obtained by integrating the ODs, which assumes well mixed behavior, to the simulation results (Figure 3.8). Scaled error was calculated as the relative error of the simulated and analytical conversion multiplied by the analytical conversion. The magnitude of the deviations decrease at longer times due to higher bulk concentrations compared to a well mixed system.
These results illustrate that maintaining a Damköhler number less than one for both components is desirable for reactions that form byproducts and when taking kinetic measurements. If the reactor dimensions do not enable this condition to be met, use of enhanced mixing will likely result in decreased byproduct formation, reaction acceleration, or extraction of more accurate kinetic data. Popular mixing techniques include the use of multilaminating devices, the use of a second phase, or premixing at low temperatures for thermally initiated reactions.

### 3.5 A simplified Damköhler number

Calculating the Damköhler number can be difficult in practice, as both an accurate estimate of the rate constant and the kinetic model is required. The Damköhler number can instead be estimated using the Fourier number and a coefficient, $\chi$, that depends on the system kinetics and feed ratios (equation 3.24).

$$Da = \frac{\chi d^2}{4\tau D} = \frac{\chi}{Fo}$$

This method allows tie lines to be plotted where $Da=1$ for different values of $\chi$ (Figure 3.9). When $\chi=1$, the expression reduces to the characteristic mixing time predicted by equation 3.13.
Operating conditions above tie lines warrant the use of premixing for the reasons previously described.

![Figure 3.9 - Tielines corresponding to Da = 1 for various values of χ.](image)

The transformations used to obtain χ are similar to the following example for a 1st order reactive system, which is given by equation 3.25 and reduces to $kt=3$ at 95% conversion. An estimate of the rate constant can be calculated as $3/t$ at high conversions, which allows for an easy method to calculate of the Dämköhler number (equation 3.26). This type of transformation was derived for several kinetic models as a function of molar feed ratio and conversion. Analytical forms for the models appear in Appendix B. While 95% conversion was somewhat arbitrarily chosen, the value of χ at different conversions may be easily calculated. Higher conversions result in more stringent requirements on mixing.

$$kt = -\ln(1 - X_f), \text{ } kt_{95\%} = 3 \tag{3.25}$$

$$Da_{1,95\%} = \frac{kd^2}{D} = \frac{3d_i^2}{4\pi D} = \frac{3}{Fo} \tag{3.26}$$

Reactions showing nonlinear inhibitions, such as systems described by Langmuir-Hingshelwood or Michaelis-Menten kinetics, do not have an analytical form of χ (equation 3.27). In these cases, initial behavior will range between a 0th and 1st order behavior depending on the values of the equilibrium constant, rate constant, and initial concentration. As such,
applying the form of $\chi$ corresponding to $1^{st}$ order reactions provides a conservative approximation.

$$R_d = \frac{KA}{1 + KA} \quad (3.27)$$

The value of $\chi$ at 95% conversion for several kinetic models appears in Table 3.3. For bimolecular systems with nonstoichiometric feeds, the most conservative (e.g. larger) value of $\chi$ should be used. In this manner, the Damköhler number for both species remains less than 1. In general, the higher the order of the reaction model, the higher the value of $\chi$. Third order reactions are uncommon, so a useful conservative estimate for $\chi$ for most systems where little is known about the kinetics is 19, which represents a second order system with equimolar feed rates.

Table 3.3 – Approximate values of $\chi$ for various kinetic models at 95% conversion. The columns correspond to the reaction order for a given species. $A_0$ and $B_0$ represent initial concentrations. # Autocatalytic in B.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>M</th>
<th>$\chi_{95%}$</th>
<th>A</th>
<th>B</th>
<th>M</th>
<th>$\chi_{95%}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
<td>0.95/$A_0$</td>
<td>1</td>
<td>1#</td>
<td>2</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>N/A</td>
<td>3</td>
<td>1</td>
<td>1#</td>
<td>4</td>
<td>0.64</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>N/A</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>200</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>N/A</td>
<td>200</td>
<td>2</td>
<td>1</td>
<td>1.1</td>
<td>90</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>19</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>16.6</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1.1</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4.7</td>
<td>1</td>
<td>-1</td>
<td>1</td>
<td>0.95</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>4</td>
<td>3.6</td>
<td>1</td>
<td>-1</td>
<td>2</td>
<td>1.97</td>
</tr>
<tr>
<td>1</td>
<td>1#</td>
<td>1</td>
<td>1.83</td>
<td>1</td>
<td>-1</td>
<td>4</td>
<td>2.48</td>
</tr>
<tr>
<td>1</td>
<td>1#</td>
<td>1.1</td>
<td>1.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.6 An analysis chart for flow systems

The Fourier number appears in the breakpoint for using a dispersion model versus laminar flow model (equation 3.6), Bodenstein number (equation 3.10), and Damköhler number (equation 3.23). This number is simple to calculate and only relies on accurate knowledge of the diffusion coefficient. For researchers with preliminary results from a flow system, calculation of
Fo and estimation of χ provide insight into what modifications may improve performance. The summarized results appear in Table 3.4, and the breakpoints correspond to the values previously described.

**Table 3.4 – Critical values of the Fourier number and χ for evaluating the impact of dispersion and mixing on a flow system.**

<table>
<thead>
<tr>
<th>Fo&lt;sub&gt;tubes&lt;/sub&gt;</th>
<th>Fo&lt;sub&gt;square&lt;/sub&gt;</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.16</td>
<td></td>
<td>use laminar flow reactor model</td>
</tr>
<tr>
<td>&lt; 2.1</td>
<td>&lt; 3.3</td>
<td>large deviations from plug flow</td>
</tr>
<tr>
<td>&lt; 21</td>
<td>&lt; 33</td>
<td>small deviations from plug flow</td>
</tr>
<tr>
<td>&gt; 21</td>
<td>&gt; 33</td>
<td>plug flow behavior</td>
</tr>
<tr>
<td>χ &lt; Fo</td>
<td></td>
<td>no premixing necessary</td>
</tr>
<tr>
<td>χ &gt; Fo</td>
<td></td>
<td>premixing advised</td>
</tr>
</tbody>
</table>

3.7 Experimental verification using a glycosylation reaction

This analysis was applied to a glycosylation reaction recently demonstrated by the Jamison group<sup>129</sup>, where a stainless steel T mixer (ID ~1.5 mm) was used in conjunction with a PTFE capillary reactor (Figure 3.10). In the study, differences in selectivity were observed depending on whether the reaction was run in 500 μm ID tubing or 750 μm ID tubing over several substrates.

![Glycosylation reaction scheme](image)

**Figure 3.10 – Glycosylation reaction scheme.** Base 1 was used in the experimental study. The major byproduct corresponded to bisalkylation of the base at the 3 position.

These results and calculated dimensionless numbers reveal that bases 3-4 only deviate slightly from plug flow behavior, yet a 7-10% lower yield of the desired product was observed
The kinetic model was predicted to be 2nd order overall based on the proposed mechanism. As the molar feed ratio of sugar to base was 1.1, a value of $\chi$ of 10.4 was used to estimate the Damköhler number, which was greater than 1 for most systems. For base 1 and base 2, large deviations from plug flow existed, and dispersion effects were potentially important. Base 1 was investigated further to demonstrate whether the previously described engineering principles could be used to enhance the performance of the system.

Table 3.5 – Comparison of reactor performance for a glycosylation reaction at different tube diameters. The dimensionless groups were calculated based on data from$^{129}$. # 500 micron ID tubing, * 750 micron ID tubing.

<table>
<thead>
<tr>
<th>Base</th>
<th>$\tau$ (sec)</th>
<th>P</th>
<th>B.P.</th>
<th>$Bo$</th>
<th>$Da$</th>
<th>$Fo$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1#</td>
<td>30</td>
<td>99</td>
<td>0</td>
<td>23</td>
<td>22</td>
<td>0.48</td>
</tr>
<tr>
<td>2#</td>
<td>300</td>
<td>80</td>
<td>6</td>
<td>230</td>
<td>2.2</td>
<td>4.8</td>
</tr>
<tr>
<td>3#</td>
<td>600</td>
<td>87</td>
<td>9</td>
<td>461</td>
<td>1.1</td>
<td>9.6</td>
</tr>
<tr>
<td>4#</td>
<td>1200</td>
<td>88</td>
<td>11</td>
<td>922</td>
<td>0.54</td>
<td>19.2</td>
</tr>
<tr>
<td>1*</td>
<td>30</td>
<td>91</td>
<td>8</td>
<td>10</td>
<td>50</td>
<td>0.21</td>
</tr>
<tr>
<td>2*</td>
<td>300</td>
<td>70</td>
<td>11</td>
<td>102</td>
<td>4.8</td>
<td>2.1</td>
</tr>
<tr>
<td>3*</td>
<td>600</td>
<td>80</td>
<td>17</td>
<td>204</td>
<td>2.4</td>
<td>4.3</td>
</tr>
<tr>
<td>4*</td>
<td>1200</td>
<td>78</td>
<td>13</td>
<td>409</td>
<td>1.2</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Due to the large Damköhler number and large deviations from plug flow, whether the bisalkylation product was caused by initial concentration gradients or from axial dispersion was not immediately clear. Three types of mixers were investigated, 1) the stainless steel T (SST) used in the initial study (Swagelok, ID: ~1.5 mm), 2) a PEEK T mixer (Idex Health and Science, ID: 0.5 mm), and 3) a custom silicon multilaminating micromixer$^{82}$ (channel width: 50 micron). Three tubing diameters were investigated (500 micron, 750 micron, and 1000 micron). As expected, use of an improved mixer resulted in faster initial rates and higher conversions (Figure 3.11). In all cases, nearly complete conversion was achieved after 30 s. The $^1$H NMR data showed no evidence of the bisalkylation product at 10 s residence time for any conditions examined.
Figure 3.11 – HPLC conversion of 5 in 1 mm ID tubing using three different mixers. The other tubing followed similar trends.

Data at partial conversion provides a more accurate representation of system dynamics. Use of a micromixer with 500 micron tubing resulted in 91% conversion, an 8% increase compared to the SST and nearly 3-fold increase in throughput compared to the initial reported values. Furthermore, even at this very high conversion, no bisalkylation product was detected. Going from 500 micron tubing to 1000 micron tubing with a micromixer resulted in an 8% decrease in conversion at a residence time of 10 s. This decrease can be strictly attributed to the flow profile within the reactor. The Fourier number for a 10 s residence time in 1 mm tubing is 0.04, which corresponds to a laminar flow model. Furthermore, the clean product purity at high conversions, even with poor mixing, gave strong indication that the bisalkylation product was in fact due to the residence time distribution within the system and not due to concentration gradients present in the system. Segmented flow is well known to introduce cross-stream mixing by recirculation in Taylor cells. Addition of nitrogen in close to a 1:1 volumetric ratio was used to effect segmented flow (Figure 3.12), which resulted in nearly identical performance across the three tube diameters and a slight enhancement relative to the single phase flow in 500 micron and 750 micron ID tubing (Figure 3.13).
Figure 3.12 – Experimental setup for effecting gas-liquid flow to reduce dispersion effects. A reactor volume of 100 μL was used for 5 and 10 s residence times, and a reactor volume of 250 μL was used for the 30 s residence time experiments.

Figure 3.13 – Experimental conversions using gas-liquid segmented flow. Results are nearly invariant to tube diameter.

Notably the $^1$H NMR at 30 s using segmented flow showed no evidence of bisalkylation product. A comparison of the sugar conversions at 10 s residence time under all mixers are summarized in Table 3.6.

Table 3.6 – Conversion at 10 s residence time using different mixing schemes. Isolated yields are in parentheses. Error on conversion is ±2% unless otherwise noted.

<table>
<thead>
<tr>
<th>ID (μm)</th>
<th>SS T</th>
<th>PEEK T</th>
<th>μmixer</th>
<th>μmixer + N2</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>83±2</td>
<td>89±1</td>
<td>91±1</td>
<td>94±1</td>
</tr>
<tr>
<td>750</td>
<td>76±2 (66)</td>
<td>89±2 (87)</td>
<td>92±1 (88)</td>
<td>93±1 (90)</td>
</tr>
<tr>
<td>1000</td>
<td>48±1</td>
<td>73±1</td>
<td>83±2</td>
<td>89±3</td>
</tr>
</tbody>
</table>

The rate constant was estimated to be 3.6±1.1 s$^{-1}$ M$^{-1}$ by least squares linear regression of the three data points obtained from the 500 micron tubing with a micromixer (Figure 3.14). No
further efforts were made specifically to determine the actual rate constant. The Damköhler number calculated using the experimental rate constant was $23\pm7$, which compares very favorably with the estimated value of 22 using equation 3.24 with an estimate of $\chi$ of 10.4.

Figure 3.14 – Comparison of experimental data using a micromixer and 500 μm tubing to predicted values using a second order model with $k = 3.6 \text{ s}^{-1} \text{ M}^{-1}$. Experimental data: $M=1.1$, $A_0 = 0.1$, $\tau = [5, 10, 30]$, $X_d (%) = [62, 90, 96]$

3.8 Experimental protocol

General reagent preparations and experimental conditions were the same as in Sniady et al., except the mixer and tubing diameters were changed while maintaining a heated reactor volume of 100 μL. Heating was applied by immersing the PTFE reactor in an oil bath, and temperature fluctuations were at most ±2°C. The reagent streams passed through a preheating coil of at least 50 μL before entering the mixer. Back pressure, 100 psig, was applied using a cartridge back pressure regulator from Idex Scientific for both the single phase and gas-liquid experiments. The back pressure regulator was not immersed in the oil bath. While the internal volume of the back pressure regulator (~130 μL) was significant relative to the reactor volume, the reaction rate was very slow at room temperature compared to under reaction conditions; diluting samples with methanol immediately upon collection proved an adequate method to quench the reaction, and
sample analysis was performed using an isocratic HPLC method (reverse phase C18 column, 85:15 Methanol:Water v/v). Product to byproduct ratios were measured using $^1$H NMR.

For the gas-liquid experiments, the gas flow rates were maintained constant and were set using a mass flow controller that was calibrated immediately before use. The reactor volume was increased to 250 µL for the 30 s residence time, which was necessary as the mass flow controller was operated near its minimum flow rate of 2 sccm. Pulsations from use of the cartridge back pressure regulator were visually noticeable; however, deviations in conversion were only slightly larger (±3%) compared to single phase experiments (±1%). The liquid streams were mixed prior to contacting nitrogen to ensure uniform slug compositions.

3.9 Conclusions

Dispersion and mixing are important factors in understanding behavior in continuous flow reactors, especially for reactions where byproducts can form or degradation can occur. Different aspects of this problem have been combined and easily calculable relationships have been derived that should serve as a reference for when either mixing or dispersion are important in a flow system. For very fast reactions, while mixing is likely the most important factor, a laminar flow reactor model may be necessary to fully understand the reactor system.

For most microchemical systems, only small deviations from plug flow are expected due to the ability of radial diffusion to compensate for a parabolic flow profile. However, scale-up by increasing tube diameter will likely require incorporation of a residence time distribution model to accurately predict performance. The feasibility of these techniques for improving processing conditions was demonstrated on a glycosylation reaction, which resulted in increased throughput by improving the initial mixing and a cleaner product profile by eliminating dispersion. Furthermore, the proposed method for estimating the Damköhler number was found to give an
excellent approximation to the traditional approach relying on accurate estimates of the rate constant.
Ch 4. Expanding the pot of thermomorphic systems using activity coefficient models

4.1 Motivation

Biphasic catalytic processes represent an important subset of industrially relevant processes. Both liquid-liquid\textsuperscript{32, 33, 106, 107} and gas-liquid-liquid\textsuperscript{158-160} catalytic processes have been developed, and a very common technique in these processes involves addition of a phase selective tag to the catalyst to improve partitioning and recycling. These processes are advantageous in that catalyst recycling may be achieved, homogeneous catalysts may be prepared and used, and catalyst separation and recovery processes rely on phase separation techniques, which are less energy intensive than distillations and easier to optimize than chromatographic separations.

The major downside of phase selective catalytic processes is the presence of a separate phase, which can result in reduced throughputs due to mass transfer within a system. Thus, processes developed at a bench scale may not be directly transferable into pilot plant or production scales without reoptimization. One of the advantages of microreactor platforms for multi-phase flows is the high surface area to volume ratio; however, throughputs in these platforms are limited and scale-up by increasing reactor diameters can result in reduced mass transfer efficiencies.

The following two examples illustrate the difficulty in achieving scalable continuous flow processes under biphasic conditions. The gas-liquid Pd-catalyzed oxidation of 1-phenylethanol to acetophenone in a 7 L (0.375” ID) continuous flow reactor required 4.5 hours to achieve full conversion compared to 45 minutes in the lab scale reactor (5 mL, 0.25” OD)\textsuperscript{104}. Similarly, mass transfer in biphasic Pd-catalyzed amination reactions was found to be critical to achieve high conversions, as the use of both tetrabutylammonium bromide as a phase transfer agent and a
column packed with stainless steel beads were necessary to achieve high yields\textsuperscript{108}. Performing the reaction in capillary tubing or without a phase transfer catalyst resulted in significantly reduced yields, and even the use of different volume reactors resulted in different behavior.

Thermomorphic solvents\textsuperscript{161} and the use of supercritical carbon dioxide (sc(CO\textsubscript{2}))\textsuperscript{162} are demonstrated techniques for eliminating phase boundaries. These systems exhibit a temperature or pressure dependent transition from multiple phases to a single phase. While most processes of interest would have an upper critical solution temperature (CST) and form a single phase upon heating, thermomorphic behavior also exists for systems with lower CSTs (Figure 4.1).

![T-x diagram of thermomorphic solvents with upper CST (left) or lower CST (right).](image)

**Figure 4.1** – T-x diagram of thermomorphic solvents with upper CST (left) or lower CST (right).

The ability to operate processes using a single phase would eliminate difficulties associated with reduced mass transfer at different scales in flow processes while maintaining the ability to separate and recover a homogeneous catalyst. Furthermore, continuous flow thermomorphic processes in microreactors are attractive due to the rapid heat transfer, which would facilitate rapid thermomorphic transitions, and the ability to perform liquid-liquid separations\textsuperscript{66,163}, which would facilitate continuous catalyst separation and recycling (Figure 4.2). As the number of thermomorphic solvents demonstrated in the literature for organic transformations is small, the
aim of this work was to expand the number of relevant organic solvent combinations through the application of thermodynamic models.

Figure 4.2 – Hypothetical thermomorphic process for hydrogenations under thermomorphic conditions with integrated gas-liquid and liquid-liquid separations.

4.2 Batch catalyst recycling using thermomorphic processes

A pioneer in the use of thermomorphic catalytic processes is David Bergbreiter of Texas A&M\textsuperscript{161, 164}. His group has demonstrated a number of thermomorphic processes using polymer-bound catalysts to enhance phase selectivity\textsuperscript{165, 166} (Figure 4.3). Hoveyda-Grubbs metathesis catalysts\textsuperscript{167, 168}, Jacobsen salen epoxide catalysts\textsuperscript{169}, and Pd-SCS pincer catalysts\textsuperscript{40} have all been successfully recycled using thermomorphic processes. In all of these examples, modification of the catalyst with a polymer was performed to control phase selectivity behavior. However, solvents used in these studies were limited to N,N-Dimethylformamide(DMF)-heptane, N,N-dimethylacetamide(DMA)-heptane, ethanol-water-heptane, or acetonitrile-heptane, which indicates a potential current limit to the knowledge of thermomorphic solvents. The ability to
perform chemistries in other thermomorphic solvents would no doubt enable additional chemical processes to be performed.

![Diagram of polymer supported thermomorphic process schematic from Bergbreiter et al.](image)

**Figure 4.3 – Polymer supported thermomorphic process schematic from Bergbreiter et al.**

Fluorous-biphasic and fluorous-thermomorphic systems have been applied to catalyst recycling, though fluorous-thermomorphic sometimes refers to solubility enhancement of precipitated catalysts upon heating; catalyst separation and recycling is achieved either by filtration or decanting the product solution. The latter types of processes would be ill suited for catalyst separation and recycling under flow conditions.

A related technique involves adjusting solvent miscibilities through the application of pressurized carbon dioxide. The so-called Organic-Aqueous Tunable Solvent (OATS) performs a reaction under homogeneous conditions, for example with tetrahydrofuran (THF)-water, and then uses sc(CO₂) to effect a decrease in mutual solubility between the solvents and cause a phase split (Figure 4.4). The platform has been applied to a hydrosoymlation reaction using a Rhodium-sulphonated triphenylphosphine complex, which was successfully recycled three times. The authors claim the technique should be applicable to a wide range of organic solvents due to the scarce solubility of CO₂ in water.
4.3 Phase stability criteria of liquid-liquid systems

For multiphase liquid-liquid systems, thermodynamic equilibrium occurs when the total internal energy in a system is minimized. The Gibbs fundamental equation in equation 4.1 can be difficult to work with due to the demands of measuring enthalpy, $H$, entropy, $S$, and activity, $\mu_i$, from a reference state and not as an absolute value. Use of a Legendre transform to convert from internal energy, $U$, to Gibbs energy, $G$, results in a more manageable form where changes to temperature, $T$, and pressure, $P$, are measured (equation 4.2). The form of Gibbs energy is frequently written in terms of enthalpy (equation 4.3) instead of internal energy (equation 4.4). Minimization of equation 4.4 for mixtures is the basis for all estimates of phase equilibrium.

\[
U = TS - PV + \sum_{i=1}^{n} \mu_i N_i \quad (4.1)
\]

\[
G = U + PV - TS \quad (4.2)
\]

\[
H = U + PV \quad (4.3)
\]

\[
G = H - TS \quad (4.4)
\]

\[\]

Variables in this chapter follow the syntax from Tester and Modell. Specifically, an underlined variable indicates dependence on system size (e.g. extensive property), and a bar above a variable indicates the property is a partial molar property. Subscripts refer to species $i$, and superscripts refer to phases.
Determination of a function minimum or maximum occurs when the first derivative of the function is zero. Minima and maxima may be distinguished by evaluation of the second derivative. The first and second derivatives of equation 4.4 appear in equations 2.5-6.

\[ dG = dH -TdS \quad (4.5) \]
\[ d^2G = d^2H -Td^2S \quad (4.6) \]

For equilibrium of multiple phases, three criterions must be satisfied. Two criteria are trivial but are included for completeness: the (1) temperature and (2) pressure in each phase must be identical. Were these criteria not satisfied, either heat transfer due to a temperature gradient or convective mass transfer due to fluid flow would occur. The most complex and interesting criterion (3) is the chemical potential of each species in each phase must be equal (equation 4.7).

\[ \mu'_i = \mu''_i \quad (4.7) \]

The chemical potential, also known as the partial molar Gibbs energy, can be related to mol fraction, \( x \). For an ideal solution, this relationship is given in equation 4.8. The function \( \Lambda \) is a general correction for a reference state of a pure component. An alternative manner to calculate Gibbs energy is by summing partial molar enthalpies and compositions (equation 4.9). Use of intensive instead of extensive coordinates allows composition to be used (equation 4.10). For an ideal solution, the total Gibbs energy may be calculated by summing the chemical potentials of each species and adding the Gibbs energy of the pure material (equation 4.11).

\[ \mu_i = \bar{G}_i = RT \ln x_i + \Lambda_i(T, P) \quad (4.8) \]
\[ G = \sum_{i=1}^{n} N_i \bar{G}_i \quad (4.9) \]
\[ G = \sum_{i=1}^{n} x_i \bar{G}_i \quad (4.10) \]
\[ G^{ID} = G_{\text{pure}}^{ID} + G_{\text{mix}}^{ID} = \sum_{i=1}^{n} x_i \bar{G}_i + RT \sum_{i=1}^{n} x_i \ln x_i \quad (4.11) \]
Solutions exhibiting phase separations are far from ideal and cannot be modeled so simply. Deviation from ideality is measured in general as an excess property (equation 4.12). In turn, excess Gibbs energy can be calculated from an activity coefficient, \( \gamma \), which varies with temperature and composition (equation 4.13). Combining equation 4.11-13 results in an expression for the Gibbs energy of a mixture in terms of activity coefficients (equation 4.14).

\[
G_i = G_i^{EX} + G_i^{ID}
\]

\[
\overline{G}_i^{EX} = RT \ln \left( \gamma_i \left( x_i, T \right) \right)
\]

\[
G = \sum_{i=1}^{n} x_i G_i + RT \sum_{i=1}^{n} x_i \ln x_i + RT \sum_{i=1}^{n} x_i \ln \left( \gamma_i \left( x_i, T \right) \right)
\]

The limit of stability for binary mixtures is that the second derivative of Gibbs energy of a system must be positive over the range of composition (equation 4.15). As the second derivative of the first term in equation 4.14 will always be zero; thus, only the ideal and excess Gibbs energy of mixing are important in predicting phase equilibrium (equation 4.16). The form of equation 4.14 is general to \( n \) components; however, the stability criterion for ternary systems is slightly different; the determinant of a matrix of the second derivatives of Gibbs energy of mixing must be positive at a given composition (equation 4.17). Thus, phase splitting for systems may be predicted with only the overall system composition and activity coefficients for each species.

\[
\frac{d^2 G_{mix}}{dx_i^2} > 0
\]

\[
G_{mix} = \sum_{i=1}^{n} x_i \left( \overline{G}_{i,mix}^{ID} + \overline{G}_{i,mix}^{EX} \right) = RT \sum_{i=1}^{n} x_i \left( \ln x_i + \ln \left( \gamma_i \left( x_i, T \right) \right) \right)
\]
\[
\begin{align*}
\frac{d^2 G_{\text{mix}}}{dx_1^2} & \frac{d^2 G_{\text{mix}}}{dx_2^2} \\
\frac{d^2 G_{\text{mix}}}{dx_1 dx_2} & \frac{d^2 G_{\text{mix}}}{dx_2^2} \\
\frac{d^2 G_{\text{mix}}}{dx_1 dx_2} & \frac{d^2 G_{\text{mix}}}{dx_2^2} \geq 0
\end{align*}
\]

Systems where this criterion is not met will exhibit phase splitting if the total system composition between both phases falls within the region of instability (Figure 4.5). Also note that metastable systems between the equilibrium concentrations and limit of stability may exist as a single phase.

Figure 4.5 – Gibbs energy for single phase (left) and multi-phase (right) binary systems.

While not done for this thesis, compositions and partition coefficients could be predicted with the data obtained in these simulations (equation 4.18). Solutions to these problems rely on the simultaneous solution of several algebraic equations.

\[
x_i x_i' = x_i x_i''
\]

(4.18)

### 4.4 Screening algorithm for binary thermomorphic solvents

With the idea of using activity coefficients in mind, a general approach to screening for binary thermomorphic solvents was developed. The approach involved calculating the Gibbs energy of mixing for a binary system over the composition range \(0.01 < x_1 < 0.99\) in increments
of 1 mol% and temperatures ranging from $0^\circ C < T < 150^\circ C$ in $10^\circ C$ increments. At each point the second derivative was either calculated analytically for the UNIQUAC simulations or numerically using center point differentiation (equation 4.17).

$$\frac{d^2G_{\text{mix},i}}{dx_i^2} = \frac{G_{\text{mix},i-1} + G_{\text{mix},i+1} - 2G_{\text{mix},i}}{\Delta x_i^2} \tag{4.19}$$

A simple search algorithm would determine whether phase separation occurred at any composition and temperature. The program would then classify the solvent combination as either completely miscible, completely immiscible, or thermomorphic depending on whether phase separation never occurred, always occurred, or only occurred under certain compositions and temperatures. To test whether this technique worked, simulations using UNIQUAC were performed for a model system, heptane-N,N-dimethylformamide (DMF). This system has been used by Bergbreiter for Heck reactions with a reported CST of $69^\circ C$. Relevant parameters for this simulation appear in Table 4.1 and the results appear in Figure 4.6. The simulated upper critical solution temperature was found to be $84^\circ C$. More details about UNIQUAC appear in section 0 of this thesis.

![Figure 4.6 - Simulation of Heptane-DMF using uniquac. Left: Gibbs energy of mixing. Right: T-x diagram.](image-url)
Table 4.1 – Heptane(1)-DMF(2) parameters for UNIQUAC simulations

<table>
<thead>
<tr>
<th></th>
<th>Heptane(1)</th>
<th>DMF(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r )</td>
<td>5.17</td>
<td>3.09</td>
</tr>
<tr>
<td>( q )</td>
<td>4.40</td>
<td>2.74</td>
</tr>
<tr>
<td>( q' )</td>
<td>4.40</td>
<td>2.74</td>
</tr>
<tr>
<td>( \Delta u_{1,2} )</td>
<td>402 K</td>
<td></td>
</tr>
<tr>
<td>( \Delta u_{2,1} )</td>
<td>-83 K</td>
<td></td>
</tr>
</tbody>
</table>

As these computations are relatively quick, a large number of solvent combinations could be screened; a total of 42 solvents were identified as being potentially interesting for organic synthesis, which is 861 binary solvent combinations. The list of solvents considered appears in Table 4.2.

Table 4.2 – List of synthetically useful solvents investigated for thermomorphic applications.

<table>
<thead>
<tr>
<th>Acetone</th>
<th>Dimethyl Sulfoxide</th>
<th>Perfluorobenzene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>N,N-Dimethylacetamide</td>
<td>Perfluoromethylcyclohexane</td>
</tr>
<tr>
<td>Amyl Alcohol</td>
<td>N,N-Dimethylformamide</td>
<td>Perfluorooctane</td>
</tr>
<tr>
<td>Benzenne</td>
<td>Dioxane</td>
<td>Perfluorotoluene</td>
</tr>
<tr>
<td>1-Butanol</td>
<td>Ethanol</td>
<td>1-Propanol</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Ethyl acetate</td>
<td>p-Xylene</td>
</tr>
<tr>
<td>1-Decanol</td>
<td>Ethylene glycol</td>
<td>Pyridine</td>
</tr>
<tr>
<td>Dibutyl ether</td>
<td>Heptane</td>
<td>t-Butyl Alcohol</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>Hexane</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>1-Hexanol</td>
<td>Toluene</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>Isopropanol</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>Disopropyl ether</td>
<td>Methanol</td>
<td>Trifluoroethanol</td>
</tr>
<tr>
<td>Diethylene glycol</td>
<td>Methyl t-Butylether</td>
<td>Trifluorotoluene</td>
</tr>
<tr>
<td>Dimethoxyethane</td>
<td>1-Pentanol</td>
<td>Water</td>
</tr>
</tbody>
</table>

4.5 Comparison of activity coefficient models

Due to the large number of solvent combinations, selection of an appropriate activity coefficient model was quite important. A number of candidate models were considered, including the non-random two liquid (NRTL), regular solution theory (RST), universal quasi-chemical activity coefficient model (UNIQUAC), Wilson, and Conductor-like Screening Model.

† Information in this section about activity coefficient models was compiled from Tester and Modell or Sandler unless a separate reference is specifically cited.
While ultimately a variant of the UNIQuac group-Functional Activity Coefficient (UNIFAC) model was selected due to its flexibility and temperature dependent parameters, a brief comparison of the models follow.

A few of the candidate models could be eliminated immediately. The Wilson model can only be used for miscible systems (equation 4.20) – differentiation of the excess Gibbs energy does not allow the possibility of an immiscible system. In this model, $A$ represents a combined volume fraction and energetic interaction parameter.

$$\frac{\bar{G}_i^{EX}}{RT} = -\ln\left(x_i + A_{i,j}x_j\right) \quad (4.20)$$

Similarly, regular solution theory does not predict negative deviations from an ideal solution, which was sufficient to exclude it as a possibility (equation 4.21). As in other models, $\phi_i$ represents a volume fraction related to the composition, $V_i$ represents the molecular volume and is species dependent, and $\delta_i$ corresponds to a solubility parameter that can be calculated from internal energy.

$$\frac{\bar{G}_i^{EX}}{RT} = V_i\Phi_j^2\left(\delta_i - \delta_j\right)^2 \quad (4.21)$$

Both the NRTL and UNIQUAC models were carefully scrutinized. These models both provide reasonable accuracy for systems with available parameters and are applicable to both liquid-liquid and single phase liquid systems. Furthermore, both models can be applied to ternary mixtures. The NRTL model for binary mixtures requires at least two and preferably three interaction parameters per binary and has no solvent specific parameters (equations 2.22-24). The parameter $\alpha$ is frequently approximated as 0.3 but can be system specific.

$$\frac{\bar{G}_i^{EX}}{RT} = (1 - x_i) \frac{\tau_{j,i}G_{j,i}}{x_i + x_jG_{j,i}} \quad (4.22)$$
The main difference between UNIFAC and UNIQUAC is that interaction parameters are calculated in the UNIFAC model by breaking each molecule into functional groups and calculating the interactions between all functional groups of a molecule as opposed to the lump parameters used by UNIQUAC. For example, di(ethylene glycol) has two hydroxyl groups, three \(-\text{CH}_2-\) groups, and one ethereal group. Ethyl acetate has one \(-\text{CH}_3\) group, one \(-\text{CH}_2-\)
group, and one acetyl group. Calculating interactions between the two molecules require knowledge of nine separate parameters for this example (Figure 4.7).

![Functional group breakdown and interactions for di(ethylene glycol) and ethyl acetate using UNIFAC.](image)

Figure 4.7 – Functional group breakdown and interactions for di(ethylene glycol) and ethyl acetate using UNIFAC.

For the purposes of screening solvent combinations for thermomorphic behavior, use of the UNIFAC method has several advantages relative to the UNIQUAC and NRTL models. One significant advantage of UNIFAC over UNIQUAC is that interactions may be estimated between molecules where experimental measurements have not been made. A variant known as the modified UNIFAC Dortmund (UNIFAC-Do) has temperature dependent interaction parameters, which should increase overall accuracy\textsuperscript{183}. As a large body of literature exists for the roughly 80 functional groups, and interaction parameters for most functional groups have been tabulated, no compilation of parameters was necessary\textsuperscript{184}. Future addition of solvents to the list would be a relatively straightforward task, whereas with either the UNIQUAC or NRTL $2N$ parameters would need to be found to add an additional solvent, where $N$ is the current number of solvents.

The UNIFAC-Do method is mathematically more complex than any of the models discussed thus far. The activity coefficients are split into combinatorial and residual components (equation 4.30), which can be related to Gibbs excess energy through equation 4.13.

$$\ln \left( \gamma_i(x_i, T) \right) = \ln \left( \gamma_i^{comb}(x_i, T) \right) + \ln \left( \gamma_i^{residual}(x_i, T) \right)$$

(4.30)

Calculation of the combinatorial activity coefficient is relatively straightforward, though the form is slightly modified from the original UNIFAC to enable calculations with compounds of
differing size (equation 4.31). The volumetric parameters, $V'_i$ and $V_i$, and surface area parameters, $F_i$, are calculated using group contributions of 1) each functional group within a molecule (equation 4.32-33) and then 2) each molecule within the mixture (equation 4.34-36). The only input for this calculation are the number, $v$, of each functional group, $l$, functional group van der Waals volume contributions, $R_i$, and functional group surface area contributions, $Q_i$.

\[
\ln \left( \gamma_i^C \right) = 1 - V'_i + \ln \left( V'_i \right) - 5 q_i \left( 1 - \frac{V'_i}{F'_i} + \ln \left( \frac{V'_i}{F'_i} \right) \right) \tag{4.31}
\]

\[
r_i = \sum_{j=1}^{m} v_j R_j \tag{4.32}
\]

\[
q_i = \sum_{j=1}^{m} v_j Q_j \tag{4.33}
\]

\[
V'_i = \frac{r_i}{\sum_{j=1}^{m} x_j r_j} \tag{4.34}
\]

\[
V_i = \frac{r_i^{3/4}}{\sum_{j=1}^{m} x_j r_j^{3/4}} \tag{4.35}
\]

\[
F_i = \frac{q_i}{\sum_{j=1}^{m} x_j q_j} \tag{4.36}
\]

Calculation of the residual activity coefficient is somewhat more complicated (equation 4.37) and is calculated on the basis of each functional group (equation 4.38). The residual contribution per functional group, $\Gamma_i$, is compared against the residual contribution in the pure material, $\Gamma_i^{pure}$. The residual contribution per functional group is calculated based on temperature dependent interactions between functional groups (equation 4.39), $\Psi_{i,k}$, mixture functional group fraction (equation 4.40), $X_i$, and specific surface area per functional group (equation 4.41), $\theta_i$. 

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Note the temperature dependent interaction parameters are not commutative (e.g., \( \Psi_{i,k} \neq \Psi_{k,i} \)), and the mixture functional group fraction for pure materials has a simplified form since the mol fraction is unity. One significant disadvantage of this method is the reliance on interaction parameters for every functional group. A single missing parameter will prevent calculation.

\[
\ln \left( \gamma_i^R \right) = \sum_{i=1}^{m} \psi_i' \left[ \ln \left( \Gamma_i \right) - \ln \left( \Gamma_i^{\text{pure}} \right) \right]
\]

(4.37)

\[
\ln \left( \Gamma_i \right) = Q_i \left[ 1 - \ln \left( \sum_{k=1}^{m} \theta_k \Psi_{i,k} \right) - \sum_{k=1}^{m} \theta_k \psi_{i,k} \right]
\]

(4.38)

\[
\psi_{i,k} = \exp \left[ - \frac{a_{i,k} + b_{i,k} T + c_{i,k} T^2}{T} \right]
\]

(4.39)

\[
X_i = \frac{\sum_{i=1}^{m} x_i \psi_i'}{\sum_{i=1}^{m} \sum_{j=1}^{n} \psi_i' x_j}
\]

(4.40)

\[
\theta_i = \frac{Q_i X_i}{\sum_{n=1}^{N} Q_n X_n}
\]

(4.41)

Out of the previously described group contribution models, the UNIFAC-Do model was the clear winner in terms of flexibility and ease of implementation. A program to perform the screening algorithm described in 4.4 was thus written in MATLAB for binary and ternary systems.

Compared to the previously described group contribution models, the COSMO-type activity coefficient models are quite new, having been developed within the past 20 years, and rely on quantum chemical calculations to estimate surface charge distributions of ideally solvated molecules\textsuperscript{186-190}. Activity coefficients and excess Gibbs energy are calculated from disturbances to the surface charge arrangements (equation 4.42).
\[ E_{\text{misfit}}(\sigma, \sigma') = a_{\text{eff}} \frac{\alpha}{2} (\sigma + \sigma')^2 \] (4.42)

One presumed advantage of COSMO type models is pre-existing structural information for calculations is not required, which results in significantly fewer adjustable parameters\(^{187}\); typically only 8 parameters are adjusted in COSMO simulations compared to the 37 parameters for the ethyl acetate-diethylene glycol system in Figure 4.7 (9 interaction parameters*3 coefficients per parameter + 5 functional groups*2 structural parameters per group). The accuracy of these models compared to group contribution methods is hotly debated in the literature\(^{191,192}\). In particular, both group contribution methods and COSMO type models with very polar compounds frequently provide erroneous results\(^{191}\). A comparison of results from COSMO models to results obtained from UNIFAC might prove an interesting future project. As databases containing the quantum information are becoming available, the initial time consuming quantum calculations should not be problematic.

### 4.6 Binary screening results

A MATLAB program consisting of two scripts and several data files was written to calculate whether a predicted solvent combination would exhibit thermomorphic behaviors. The .m files appear in Appendix D and are described in detail here. Interaction parameters and functional group parameters were obtained from the UNIFAC consortium website, which had tabulated data from several published sources\(^{184}\). Bold titles indicate a program title; the .m indicates the program is written for MATLAB.

1. **TSS_Unifac.m** – main program for performing the calculations described in 2.30-41. Binary interaction parameters and structural parameters are imported into memory from external data files. Calculations of residual and combinatorial activity coefficients are performed using two internal sub-functions. Plots of Gibbs energy
and T-x diagrams are generated, and the solvent combination being tested is classified as biphasic, miscible, or thermomorphic.

2. **unifac_screen.m** – shell program that calls **TSS_Unifac.m** when performing the combinatorial screen. Sorts results and outputs lists of completely miscible, completely biphasic, and thermomorphic solvent combinations.

The binary screen was successful with 861 solvent combinations being performed at temperatures from 0-150 °C in ~20 minutes on a single laptop computer. The summarized outputs appear in Figure 4.8. A total of 43 solvents were predicted to be thermomorphic (Table 4.3), and additional 44 solvents were predicted to be completely biphasic (Table 4.4).

<table>
<thead>
<tr>
<th>Compound 1</th>
<th>Compound 2</th>
<th>Compound 1</th>
<th>Compound 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetonitrile</td>
<td>1-Decanol</td>
<td>Dimethylacetamide</td>
<td>Heptane</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>Ethylene glycol</td>
<td>Dimethylacetamide</td>
<td>Hexane</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>Heptane</td>
<td>Dimethylformamide</td>
<td>Heptane</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>Hcxane</td>
<td>Dimethylformamide</td>
<td>Hexane</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>t-Butyl Alcohol</td>
<td>Dimethylformamide</td>
<td>Triethylamine</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>Water</td>
<td>Ethanol</td>
<td>Heptane</td>
</tr>
<tr>
<td>Benzene</td>
<td>Perfluoromethylcyclohexane</td>
<td>Ethanol</td>
<td>Perfluorobenzene</td>
</tr>
<tr>
<td>Benzene</td>
<td>Perfluoroctane</td>
<td>Heptane</td>
<td>Methanol</td>
</tr>
<tr>
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<td>Diethylene glycol</td>
<td>Heptane</td>
<td>Perfluoromethylcyclohexane</td>
</tr>
<tr>
<td>1-Decanol</td>
<td>Dichloroethane</td>
<td>Heptane</td>
<td>Perfluoroctane</td>
</tr>
<tr>
<td>1-Decanol</td>
<td>Diethylene glycol</td>
<td>Heptane</td>
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</tr>
<tr>
<td>Dibutyl ether</td>
<td>Pyridine</td>
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<td>Methanol</td>
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<td>Dichloroethane</td>
<td>Diethylene glycol</td>
<td>Hexane</td>
<td>Perfluoromethylcyclohexane</td>
</tr>
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<td>Dichloroethane</td>
<td>1-Hexanol</td>
<td>Hexane</td>
<td>Perfluoroctane</td>
</tr>
<tr>
<td>Diethyl ether</td>
<td>Pyridine</td>
<td>Hexane</td>
<td>Pyridine</td>
</tr>
<tr>
<td>Diisopropyl ether</td>
<td>Pyridine</td>
<td>Isopropanol</td>
<td>Perfluorobenzene</td>
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<td>Diethylene glycol</td>
<td>Dimethoxeythane</td>
<td>Methyl t-Butylether</td>
<td>Pyridine</td>
</tr>
<tr>
<td>Diethylene glycol</td>
<td>Dioxane</td>
<td>Perfluorobenzene</td>
<td>1-Propanol</td>
</tr>
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<td>Diethylene glycol</td>
<td>Ethyl acetate</td>
<td>Perfluoromethylcyclohexane</td>
<td>Trifluorotoluene</td>
</tr>
<tr>
<td>Diethylene glycol</td>
<td>Tetrahydrofuran</td>
<td>Perfluoroctane</td>
<td>Trifluorotoluene</td>
</tr>
<tr>
<td>Dimethoxeythane</td>
<td>Pyridine</td>
<td>t-Butyl Alcohol</td>
<td>Water</td>
</tr>
<tr>
<td>Dimethoxeythane</td>
<td>Water</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 4.8 - UNIFAC binary screening results. Results are color coded based on predicted behavior.
Unfortunately, a significant fraction of compounds were unable to be calculated: 226 in total, or 26%. Inspection of Figure 4.8 reveals these compounds were generally either partially fluorous or contained a very polar compound. The inability to predict fluorous interactions was disappointing, as several of these compounds are known to exhibit thermomorphic behavior\textsuperscript{193}. Worth mentioning is that use of COSMO-type models would not have experienced the problem due to a lack of interaction parameters; interactions between compounds with known σ-profiles may be calculated\textsuperscript{187}.

The predicted $T$-$x$ diagrams for several solvents revealed that the thermomorphic behavior would not be synthetically useful. For example, diethyl ether-pyridine (110°C), methyl $t$-butyl ether-pyridine (110°C), and heptane-pyridine (70°C) were predicted to have lower CSTs, which aren’t as synthetically useful as systems with upper CSTs. Separations would have to be
performed at high temperatures, for example. Other predictions, such as chloroform-diethylene glycol and dichloroethane-1-hexanol, had very small envelopes (Figure 4.9), which indicated separation efficiencies would be low, or more likely the thermomorphic behavior would not exist. None of the systems in this paragraph were tested for accuracy.

![T-x diagram using UNIFAC](image)

Figure 4.9 — Predicted T-x diagrams using UNIFAC of chloroform-diethylene glycol (left) and dichloroethane-1-hexanol (right).

Several systems agreed experimentally with predicted performance. For example, heptane in combination with both methanol (MeOH) and acetonitrile (ACN) were found to match the predictions and were found to exhibit thermomorphic behavior. At the time this work was performed, the ACN-heptane combination had not been demonstrated as a synthetically useful combination for catalyst recycling\textsuperscript{167}. The predicted CST for ACN-heptane using UNIFAC-Do was close to 100°C, whereas the experimentally measured CST was measured at 82°C. A similar degree of accuracy was found for MeOH-heptane and DMF-heptane (Table 4.5). Comparisons of the predicted CSTs using UNIFAC and UNIQUAC reveal UNIQUAC was closer to reality compared to UNIFAC (Figure 4.10), which is in line with general predictions regarding accuracy from the Dortmund Data Bank (Figure 4.11).
Figure 4.10 – Comparison of DMF-heptane T-x diagrams using UNIFAC (left) and UNIQUAC (right).

Figure 4.11 – Relative accuracy of VLE data from 1362 data sets from the UNIFAC consortium\textsuperscript{194}.

Some systems were erroneously reported as being thermomorphic; for example, both dimethoxyethane-water and ACN-water are completely miscible at room temperature but are predicted to have a CST close to 85°C. These errors seem to be systemic, affecting primarily very polar compounds. As polar compounds are known to give difficulties for current models\textsuperscript{191}, these errors are not surprising.

Table 4.5 – Comparison of CSTs predicted using UNIFAC and experimental results.

<table>
<thead>
<tr>
<th>Compound 1</th>
<th>Compound 2</th>
<th>UNIFAC (°C)</th>
<th>Experimental (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heptane</td>
<td>DMF</td>
<td>120</td>
<td>69\textsuperscript{179}</td>
</tr>
<tr>
<td>Heptane</td>
<td>ACN</td>
<td>100</td>
<td>82</td>
</tr>
<tr>
<td>Heptane</td>
<td>MeOH</td>
<td>80</td>
<td>50</td>
</tr>
</tbody>
</table>
Thermomorphic behavior was experimentally confirmed in several synthetically useful solvent systems under continuous flow conditions. Pure solvents were fed into a microreactor, and the device was heated until a phase transition occurred using either a cartridge heater (McMaster Carr) or Peltier TE Module (TE Technology, Inc. www.tetech.com). Composition was controlled by setting flow rates on a syringe pump and could be rapidly changed. For steady state operation, no significant difference exists between the cartridge heater or TE module; temperature gradients of a few degrees have been calculated using COMSOL for the type of reactor used; however, for transient studies, such as this one, the TE module was superior due to the larger contact area between the chip and heater. Use of a cartridge heater resulted in location specific transitions from a two phases to a single phase, whereas use of a TE module resulted in nearly uniform transitions.

As the residence time for these experiments within the microreactor was 30 seconds to 10 minutes, whether the time scale of phase formation was longer than the residence time was a possibility; however, as predictions obtained using this technique rely on compositions being past the limit of stability and not at equilibrium, phase formation should occur rapidly due to supersaturation. Once a second phase forms, however, equilibration should be rapid due to the very rapid interfacial mass transfer in Taylor flow in microfluidic systems. Furthermore, while this analysis does not completely preclude phase formation from being missed, solvent combinations with long time scales for coalescence or phase splitting would not be synthetically useful.

For fluid entering a silicon microfluidic device, the thermal entrance region was calculated to be a few mm using equation 4.43; thus, thermal equilibration occurs rapidly, which is advantageous for these studies compared to bulk macrofluids in flasks or vials.
For heptane-DMF, Rhodamine dye was used to assist visualization and was soluble only in DMF. The reactor effluent was successfully separated using a Zefluor PTFE membrane with the less polar phase (e.g. heptane) wetting and permeating the membrane. Phase transitions occurred through two stages. For transitions from two phases to a single phase, an initial reduction in surface tension results in a transition from segmented to annular flow before complete disappearance of the phase boundaries (Figure 4.12). The same transition was observed to occur in reverse when going from two phases to a single phase (Figure 4.13). The manner in which these transitions occur also indicate that local compositions are not uniform immediately after a phase transition occurs (Figure 4.14). Instead, concentrations gradients initially exist, which could affect the kinetics of very fast reactions.

Figure 4.12 – Still images of a thermomorphic transition of DMF-heptane from a single phase to two phases under flow conditions. Fluid is flowing from right to left. Flow rates of DMF and heptane are both 100 μL/min. Top: Just before the transition begins. Second row: Taylor slugs are beginning to disappear. Third row: Annular flow developing. Fourth row: Thinning of the interface at the wall. Bottom row: Single phase flow.
4.7 Tunable ternary thermomorphic solvents

At least one ternary thermomorphic system has been demonstrated for catalytic applications. Ethanol (EtOH) and heptane are normally completely miscible, yet the addition of 5 vol% water results in thermomorphic behavior with a transition temperature of $\sim 80^\circ\text{C}$\(^{40}\). As only results using 5 vol% water were reported, we became interested in the effect of volume % water on the thermomorphic behavior. Perhaps addition of a third component could be used to induce
thermomorphic behavior in other solvent systems. Such behavior could be represented as overlapping ternary phase envelopes at different temperatures (Figure 4.15). Knowledge of the phase diagrams should assist with selecting biphasic feed compositions (e.g. $T_1$) that would exist as a single phase under processing conditions (e.g. $T_4$). The UNIFAC-Do software was thus extended to include ternary platforms.

Figure 4.15 – Overlapping T-x ternary diagrams that change as a function of temperature.

As the number of ternary combinations out of 42 solvents is 11,480, no automated approach was instituted. Instead, a separate program interface was developed to calculate ternary plots based on user inputted solvent combinations. Each ternary combination took ~30 s to calculate on a single laptop computer. As simulation results are displayed in terms of mol fraction, consideration must be taken into account when interpreting the diagrams. The high concentration of neat water compared to other solvents implies moderate water mol fractions are small volume fractions (Table 4.6).

<table>
<thead>
<tr>
<th></th>
<th>Water</th>
<th>Heptane</th>
<th>DMF</th>
<th>MeOH</th>
<th>EtOH</th>
<th>Hexanol</th>
<th>Toluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW (g/mol)</td>
<td>18.0</td>
<td>100.2</td>
<td>73.1</td>
<td>32.0</td>
<td>46.1</td>
<td>102.2</td>
<td>92.1</td>
</tr>
<tr>
<td>$\rho$ (g/cm$^3$)</td>
<td>1.0</td>
<td>0.684</td>
<td>0.944</td>
<td>0.792</td>
<td>0.789</td>
<td>0.814</td>
<td>0.867</td>
</tr>
<tr>
<td>$M$ (mol/L)</td>
<td>55.6</td>
<td>6.8</td>
<td>12.9</td>
<td>24.8</td>
<td>17.1</td>
<td>8.0</td>
<td>9.4</td>
</tr>
</tbody>
</table>
In the case of the water-heptane-ethanol case used by Bergbreiter and co-workers\textsuperscript{40}, the mol fractions of 5 vol\% water was calculated to be 20\%. Increasing the fraction of water to 10 vol\% corresponds to a molar fraction of 35\% water (Table 4.7).

Table 4.7 – Composition of water-ethanol-heptane ternary mixtures.

<table>
<thead>
<tr>
<th></th>
<th>vol%</th>
<th>mol %</th>
<th>vol %</th>
<th>mol %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>5</td>
<td>20</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>Ethanol</td>
<td>45</td>
<td>25</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Heptane</td>
<td>50</td>
<td>55</td>
<td>50</td>
<td>22</td>
</tr>
</tbody>
</table>

Calculation of the ternary system comprising water-ethanol-heptane revealed that increasing mol fraction of water would cause a change in CST and would likely result in loss of thermomorphic behavior. The predicted CST at with 5 vol\% water was close to 90°C, which is in reasonable agreement with the experimental temperature of 80°C. Biphasic conditions were predicted using the UNIFAC model and were experimentally realized with 10 vol\% water (Figure 4.16).

![Ternary diagram of water-ethanol-heptane. Experimental data point is reported as a red dot and corresponds to literature transition temperature reported by Bergbreiter et al.\textsuperscript{40}. The black dot corresponds to 10 vol\% water.](image)

Other ternary solvent systems were investigated, and a general paradigm of one pair of biphasic solvents in combination with a mutual co-solvent was discovered. In the previous water-ethanol-heptane example, ethanol would be considered the mutual co-solvent.
Furthermore, these ternary systems were found to have tunable CSTs – control over the amount of the mutual co-solvent had a large impact on the transition temperature. For example, the transition temperature of DMF-heptane-dioxane could be tuned from 72°C as 32°C by adjusting the composition of dioxane. UNIFAC predictions for this system were reasonable (Figure 4.17). Similarly, use of toluene was found to effect the tuning parameters of DMSO-heptane from above 80°C to 40°C. This particular combination is especially attractive, as the bulk mixture has a significant volume % of toluene (Figure 4.18). For the DMSO-heptane combination, use of dioxane instead of toluene was found not to induce thermomorphism. Conversely, for DMF-heptane, use of toluene instead of dioxane resulted in a sharp decrease of CST - 7 vol% heptane resulted in a decrease in CST from 72°C to 51°C. These results demonstrate the importance of screening co-solvents. Toluene-dioxane-ethylene glycol was found to be tunable over the range 35 – 81°C by increasing dioxane composition, though UNIFAC predictions for this system were significantly off, likely due to errors from ethylene glycol (Figure 4.19).

Figure 4.17 – Effect of composition on CST for DMF-heptane-dioxane systems. Left: Effect of CST for DMF-heptane with increasing dioxane composition. DMF and heptane flow rates were held constant at 50 µL/min each. Right: UNIFAC predicted ternary with overlaid experimental CSTs. Temperature envelopes are in 10°C increments ranging from 0°C at the top (blue) to 100°C at the bottom (red).
Ternary solvents containing large water concentrations are important for enabling thermodromorphic processes containing or forming salt byproducts. A variant of the water-ethanol-heptane solvent system was discovered which was both generalizable and tunable. Specifically, replacement of heptane with 1-hexanol resulted in significantly improved thermodromorphic behavior (Figure 4.20). Use of methanol as the co-solvent was possible, and adjustment of the chain length of the longer chain alcohol was also possible. For example, the system
1-butanol-water-ethanol had a CST of 35°C with 38.5 vol% water and 100 mg/mL sodium chloride dissolved (1.7 M) in the aqueous feed stream. This particular class of thermomorphic solvent, comprising a long chain alcohol, water, and a short chain alcohol, should be broadly tunable and is potentially applicable for coupling reactions, though the impact of high concentrations of dissolved salts is difficult to predict using UNIFAC and will likely require experimental screening.

In collaboration with Everett O’Neal, additional ternary solvents were discovered that contain reasonable volume fractions of water. These results were obtained through analysis of Hansen solubility parameters, which suggests other thermodynamic approaches besides activity coefficient models should be applicable for predicting thermomorphic solvents. The UNIFAC predicted ternary T-x plots for two systems, water-ethanol-ethyl acetate (30 vol% water, CST of 80°C) and water-DMF-ethyl acetate (33 vol%, CST of 80°C), are produced here for completeness.
Figure 4.21 – Effect of composition on water-ethyl acetate ternary systems. Left: UNIFAC predicted ternary diagram of water-DMF-ethyl acetate. Right: UNIFAC predicted ternary diagram of water-ethanol-ethyl acetate. Temperature envelopes are in 10°C increments ranging from 0°C at the top (blue) to 100°C at the bottom (red).

4.8 Evaluation of thermomorphic processes

Thermomorphic processes offer the ability to operate under homogenous conditions while enabling biphasic catalyst recycling. As homogeneous flow conditions are significantly easier to scale-up compared to biphasic conditions, these processes offer significant advantages. However, these advantages are tempered by several challenges that are potentially difficult to overcome for realizable, robust processes.

A major challenge with Pd-catalyzed coupling chemistries is the formation of an inorganic salt byproduct. These byproducts mandate the use of a thermomorphic solvent containing water to prevent precipitation, yet at the same time the presence of salts adversely affect phase miscibility. A common organic workup technique, for example, is to use saturated sodium chloride solutions to extract residual water from organic solvents, as the presence of the salts reduces the dissolved water concentration in the organic phase. The effect of byproduct formation both on phase miscibility and overall solubility can be difficult to predict but must be considered. Implementation of thermomorphic processes for reactions involving inorganic salts may be difficult to implement.
Solvent effects can have a strong impact on reaction kinetics – for example, many organometallic reactions are inhibited by coordinating solvents, such as THF or dioxane\(^5\). Thus, the use of thermomorphic solvent containing coordinating solvents would be infeasible for metathesis applications. To generalize this example, maintaining catalyst activity in non-ideal solvents is a potential challenge.

Achieving high levels of catalyst separation from the product is a potential issue. While addition of phase-tagged moieties, such as polymers or fluorous-groups is a demonstrated approach to enhance retention, design and synthesis of specialty catalysts incurs additional costs. For organocatalytic applications that require high catalyst loadings or for expensive, yet robust, catalysts, the additional cost may be worthwhile. However, the economic benefit must exceed the additional cost to be practical.

### 4.9 Conclusions

Thermomorphic solvent systems were identified as a potential mechanism for catalytic processes under flow conditions. These solvents enable single phase operation, which facilitates scale-up, and multi-phase separations. As the number of synthetically useful solvent systems in the literature is somewhat limited, a screening program using UNIFAC-Do was created, which resulted in the identification of a few synthetically useful binary systems. This approach is the first use of thermodynamic models to screen solvent combinations for thermomorphic behavior. Results from the simulations were experimentally verified under flow conditions; this work also demonstrates the potential for microfluidic devices as tools for obtaining thermodynamic data.

The most useful results of the simulation were the identification of ternary solvent systems with tunable critical solution temperatures. Several ternary combinations were identified, and the composition of these solvents can be generalized to consist of a biphasic solvent system and a
solvent miscible with both phases. These tunable solvents offer the potential to control the CST of a mixture, which may be useful for reactions that exhibit side product formation or if catalyst deactivation occurs above a certain temperature.

Experimental considerations reveal implementation of thermomorphic processes to be difficult. Several factors, including solute effects on miscibility gaps and selective phase partitioning of both the catalyst and product, are challenging to predict but are critical to successful implementation. Thus, thermomorphic processes will likely remain a niche approach to catalyst recycling but will be very powerful when successfully implemented.
Ch 5. Evaluation of fluorous physisorption as a catalyst immobilization technique for flow systems†

5.1 Motivation

Traditional catalyst immobilization techniques on heterogeneous supports rely either on covalent grafting of a modified ligand-metal complex to a support or impregnation of a metal directly in a support. These pseudo-permanent immobilization techniques are well suited to continuous flow conditions but can suffer from the inability to regenerate deactivated catalysts. Spent catalysts can be discarded and replaced by fresh catalysts after a filtration when performing batch reactions; however, replacement of deactivated catalysts under continuous flow conditions can require parallel beds, complicated valving schemes, and manual replacement of catalyst cartridges, which can be labor intensive if catalyst deactivation occurs rapidly. The ability to immobilize a catalyst using non-covalent interactions might be attractive in this context, as deactivated catalysts simply could be washed off, and a solution containing fresh catalyst could be passed over the support.

A second area where non-covalent interactions might be attractive is for immobilized catalyst screening applications. Certain catalyst families exhibit changes in reactivity based on slight changes in structure. One example of these families is the biaryldialkylphosphine ligand family developed by the Buchwald group for Pd-catalyzed aminations. Use of specific ligands have been found to selectively promote the amination of only primary amines or secondary amines. Alternatively, ligand control over the formation of 5, 6, or 7 membered rings has been

† Parts of this chapter were done in close collaboration with Lars Johansen, who at the time was a visiting master’s student at MIT from Technical University of Denmark. Dr. Damian W. Young, who at the time was a group leader at the Broad Institute, Michele Melchiore, who at the time was a doctoral student at the Broad Institute, and Dr. Marvin Yu, who at the time was Vice President of Fluorous Technologies, Inc. synthesized and provided catalysts used in this study.
demonstrated in a tandem amination-cyclization reaction. The ability to screen a family of catalysts or ligands against a single substrate or multiple substrates against a single catalyst would be attractive, especially if the temporary immobilization scheme enabled recovery of the catalyst at the end of the process.

Such an immobilization scheme would ideally meet the following requirements:

1. A large partition coefficient of the catalyst for the support relative to the solvent.
2. Some means of solubilizing the catalyst.
3. No loss of catalytic activity during loading or while running the reaction.
4. A facile means of removing the catalyst.
5. An inert support that will not adversely affect reaction conditions.

A number of non-covalent immobilization techniques meet some of these criteria and have been used in batch experiments. A careful analysis of these techniques reveals that fluororous physisorption shows the most promise as a general immobilization technique for flow systems.

5.2 Evaluation of non-covalent immobilization techniques

A thorough review of non-covalent immobilization techniques that have been used in batch studies was prepared by Horn et al. This section summarizes their work while adding thoughts relevant to continuous flow processes. Supported aqueous-phase catalysis (SAPC) is one method that uses a thin layer of a hydrophilic liquid on a hydrophilic support in conjunction with a water-soluble ligand and a nonpolar reagent and substrate. This technique has been used to effect several reaction types, including hydroformylations, Sonogashira cross-couplings, and Heck reactions. As the catalyst is initially pre-wet with a polar solvent, such as water or ethylene glycol, mass-transfer into the liquid film can be limiting; the presence of the solid support can assist in distributing the catalyst over a higher surface area to facilitate
access to catalytic sites, as was observed using sulphonated-BINAP ligands in a study performed by Wan and Davis\textsuperscript{210}.

A related technique to SAPC uses a polar support without the thin film of polar solvent. This immobilization technique relies strictly on hydrogen bonding, which limits the utility to non-polar aprotic solvents, such as dichloromethane. Epoxidations\textsuperscript{211,212}, cyclopropanations\textsuperscript{211}, and hydrogenations\textsuperscript{213-215} have all been investigated. In each case, the supported catalyst showed reduced activity relative to the homogeneous catalyst. The opposite case, where a nonpolar catalyst is adsorbed to a nonpolar support, has also been applied. For example, immobilization of Pd-triphenylphosphine on reverse phase silica gel resulted in good activity in Suzuki and Heck reactions but was limited to polar reagents\textsuperscript{216}.

The techniques outlined above rely on specific surface interactions to retain a catalyst and are limited in their generality to solvents and substrates displaying the opposite polar disposition. In particular, the inability to use reagents and solvents that have the same polarity is a significant disadvantage. Furthermore, polar supports with hydroxyl group could cause unwanted side reactions, which could cause techniques using polar supports to fail condition 5 outlined above. Lastly, the degree of partitioning of the catalyst onto the support could be an issue for all of the above techniques, particularly for solvents of middling polarity, such as THF or toluene.

Fluorous-fluorous interactions have been used in a number of examples for catalyst recovery, notably through solid phase extraction, where after the reaction is performed, the catalyst, or substrate, is separated from the reaction material based on preferential adsorption to fluorous silica gel or even Teflon\textsuperscript{®} tape (Figure 3.1)\textsuperscript{217-220}. The working phenomenon is actually the same in this case as in the previously described cases. However, fluorous-organic and fluorous-aqueous systems frequently form two phases\textsuperscript{193}, which indicates fluorous-tagged catalysts have
the potential to have stronger interactions with fluorous supports in a wider variety of solvents compared to either hydrophilic-hydrophilic or hydrophobic-hydrophobic systems. The feasibility of fluorous physisorption as a catalyst immobilization technique under flow conditions was thus investigated.

![Figure 5.1 - Fluorous solid phase extraction of dyes from Zhang et al.](image)

5.3 Packed-bed microreactor design, fabrication, and performance

A number of microreactors for studying heterogeneous catalysis have been designed and fabricated both within our group\textsuperscript{109-112} and in other groups\textsuperscript{120, 221-224}. For this project, a new silicon packed-bed microreactor was designed and fabricated. As previous designs in the group had focused on gas-phase chemistry with residence times of seconds, the size of the current design was increased to accommodate longer residence times. The reactor was fabricated from 1 mm thick single side polished or double side polished silicon wafers using standard fabrication techniques\textsuperscript{82}. The desired etch depth of 600 microns was achieved using deep reactive ion etching. Two masks, one for the front and a second for the ports, were used, and Si-rich silicon nitride was deposited on the wafer prior to anodic bonding to 1 mm thick sodium borosilicate glass. The masks appear in Appendix E, and the devices appear in Figure 5.2. The salient features of the design are:
1) microfabricated posts with 25 micron spacing for particle retention,

2) compression packaging using o-rings and a glass plate, which enables reactors to be changed in minutes,

3) large (1 mm) inlets and outlets to facilitate particle loading and unloading,

4) widths ranging from 2 mm to 10 mm, corresponding to unpacked volumes of 40 to 180 μL, to enable facile testing of different residence times while maintaining reasonable flow rates,

5) a depth of 600 micron would allow for edge effects on fluid flow to be neglected for catalyst particles with diameters of 60 micron or smaller, and

6) a uniform die size for all devices of 16 mm wide by 42 mm long. A minimum of 3 mm of silicon was left between etched features and the edge of the die.

The packaging chuck was fabricated by the MIT machine shop or by FH Peterson Machine Corporation in Stoughton, MA. Schematics for the chuck appear in Appendix F. The bottom piece was fabricated from stainless steel to increase chemical compatibility, and fluidic connections were made using threaded 10-32 coned ports. The reactor sat in a 0.5 mm deep milled slot that was 17 mm x 43 mm. The additional 0.5 mm in each direction facilitated quick alignment of the device to the ports. Fluidic seals between the reactor and chuck were made with size 005 o-rings. These grooves were milled slightly shallower than the thickness of the o-ring to enable compression of the reactor on the o-ring and not the stainless steel chuck. Two holes were drilled parallel to the reactor through the side of the chuck; the first fit a ¼” cartridge heater for heating, and the second was fitted with 10-32 barbed fittings to enable cooling fluid to be pumped through the device. In addition to the two ports and two cartridges, a thermocouple hole was drilled to allow direct thermal contact with the silicon reactors.
The top piece of the packaging chuck was fabricated from aluminum to minimize the fabrication cost. A plate of glass was used to provide uniform compression of the reactor while maintaining visibility. Twelve evenly spaced bolts were used to connect the top and bottom pieces of the chuck. The visible window in the initial design was the same size as the die; later designs reduced the visible window to increase the tolerance of the glass plates, which were manually cut using a die saw and only had tolerances of a few millimeters. Switching reactors
was possible in minutes by removing only a single screw at the top of the bed; complete
disassembly of the reactor was not necessary.

Figure 5.3 – Rendering of packaging chuck with labeled components. The channel for cooling fluid
is not shown but would be parallel to the cartridge heater.

The packed beds proved to be a robust design at low pressures with inorganic supports. Back
pressure up to 105 psi was achievable in the 2 mm wide beds. Higher pressures were not tested.
Temperatures in excess of 130°C were achieved using the design. Furthermore, particles smaller
than the weir were found to be retainable through the use of a small layer of glass beads (50
micron) as an additional weir (Figure 5.4).

Figure 5.4 – Secondary weir of glass beads for immobilization of particles smaller than 25 μm.
Photo courtesy of Dr. Xiaoying Liu.
Techniques for loading both slurries and dry particles were developed. To load slurries, particles were suspended in a solvent by immersion in an ultrasonic bath immediately before loading the particles into a syringe. The slurry was then manually injected into the reactor. This technique was inefficient due to particle interactions with the walls of the syringe or tubing and gravitational settling in the syringe. Replacing the syringes or tubing would be necessary when this happened. Typically 4-6 attempts were needed to fill a bed, which could require in excess of 20 minutes and resulted in significant loss of material.

Fluidization of dry particles using vacuum was significantly more effective. Particles could be loaded into a syringe, which would then be connected to the reactor using a luer; alternatively, tubing could be inserted directly into a vial containing the particles. Fluidization was accomplished either through use of a vacuum pump or by manually pulling on a 10 mL plastic syringe. Dry particle loading using vacuum requires only seconds. Use of 1 mm ID tubing is recommended for both techniques to minimize contact of the particles with the walls.

Unloading the microreactor involved completely drying the bed by passing pressurized nitrogen through the reactor. The flow of the gas through the bed was reversed, and the particles were blown out. Pressure pulses by rapidly compressing a 5 or 10 mL plastic syringe were frequently more effective than a constant stream of gas. Occasionally use of alternating pressure pulses and liquid pulses were necessary to completely empty the reactor; sonication of the device was rarely required. Recovery in this manner facilitated analysis of spent catalyst materials. Despite the use of a 1 mm wide port, removing polymeric material from the reactor was more difficult than inorganic material, as the polymer particles tended to agglomerate.

The current design did have limitations which could be improved upon. Use of high pressures with wider beds (8-10 mm) would occasionally result in a bed cracking along the
sodium borosilicate-silicon wafer bond. Future designs for larger volumes should incorporate parallelization of multiple 2-4 mm wide channels to reduce failure rates. These devices were not well suited for polymeric materials, as swelling caused a number of devices to fail. Either pre-swelling the beads or loading the bed differentially using the slurry technique was necessary (Figure 5.5).

![Figure 5.5 - Microfabricated bed loaded with catalytic polystyrene beads. The beads shrank after loading due to a switch of solvents, which resulted in reduced contact between the fluid and catalyst.](image)

Another manner in which devices occasionally failed was by cracking along the walls on the silicon side. This type of failure seemed to be wafer specific and would occur if the etch depth along the walls was too deep. As non-uniform, accelerated etching can sometimes occur along the walls, measuring the depth at the corners instead of the center of the cavity or use of a thicker wafer should prevent this type of failure.

Another cause of reactor failure was due to o-ring swelling if an incompatible solvent was used. As the cost per wafer of deep reactive ion etched wafers is in the thousands of dollars, use of relatively expensive perfluoropolymer Kalrez o-rings ($25, McMaster Carr) made economic sense. Kalrez o-rings were used for the majority of the studies in this thesis and are recommended for most applications.
5.4 Fluorous-tagged phosphine oxide retention on fluorous silica gel

Determining whether fluorous-fluorous interactions were strong enough to retain a catalyst required was an important step in demonstrating the feasibility of fluorous physisorption as an immobilization technique in flow. As fluorous-tagged materials can be costly, require special synthesis and purification steps, and be limited in availability, this initial study was performed using a less expensive fluorous-tagged phosphine oxide derivative (Diphenyl-[4-(1H,1H,2H,2H-perfluorodecyl)phenyl] phosphine oxide, F017057, Fluorous Technologies, Inc.). The inline UV-vis setup described in detail in chapter 2 of this thesis was used to measure retention of the fluorous phosphine oxide species.

A typical retention experiment involved injecting a pulse of the fluorous-tagged phosphine oxide, 2.5 μL of 2.5 mM, into a carrier stream of the solvent of interest. The solvent was passed through the previously described packed bed microreactors containing FSG. Absorption at 265 nm was used to monitor the phosphine oxide concentration. The time of injection was recorded, and the experiment was carried on until the absorbance had returned to the base level (Figure 5.6). Methanol, hexanol, dimethylsulfoxide (DMSO), water, and heptane were selected as candidate solvents for initial investigation. A small amount of methanol (5 vol%) was necessary to solubilize the tracer when using DMSO. For heptane and water, injection of the tracer in a carrier stream of DMSO:methanol (95:5 v/v) was necessary due to the poor solubility of the tracer in water. The solvent was then quickly switched from DMSO to either heptane or water (Figure 5.7). For these two cases, no change from the baseline was observed after three hours; switching solvents again to DMSO resulted in elution at only slightly shorter time than if pure

† These experiments were performed in close collaboration with with Lars Johansen, who at the time was a visiting master’s student at MIT from Technical University of Denmark.
DMSO had been used, which indicated that fluorous-fluorous interactions were very strong relative to water or heptane. The difference in retention time between the two cases was approximately 600 seconds, though both peaks were quite broad.

![Absorbance vs. Time](image)

**Figure 5.6** – Retention of fluorous-tagged phosphine oxide derivatives in methanol, hexanol, and DMSO.

![Absorbance vs. Time](image)

**Figure 5.7** – Switching experiment of fluorous-tagged phosphine oxide in water and DMSO. Left: Overlay of DMSO experiment with switching experiment. Right: Comparison of peak retention time between the two cases after removing the water phase.

The bulk residence time, \( \tau \), was calculated as the ratio of the volumetric flow rate, \( Q \), and a previously measured volume, \( V_{void} \) (equation 5.1). The ratio of the retention time, to the bulk fluid residence time corresponds to the number of column equivalents (NCE) of solvent necessary to remove 50% of the tracer (equation 5.2). For the solvent switch experiments of
heptane and water, the NCE of the pure solvent was calculated based on the ratio of DMSO retention to the duration of only water flowing (equation 5.3).

\[
\tau = \frac{Q}{V_{\text{void}}}
\]

\[
NCE = \frac{\tau}{t} = \frac{V_{\text{void}}}{Q} \int C(t) dt
\]

\[
NCE_{H_2O\ only} = \frac{t_{H_2O}}{\tau} \frac{NCE_{\text{DMSO\ switch}}}{NCE_{\text{DMSO\ only}}}
\]

The advantage of using the dimensionless NCE as a comparison tool is that different solute-solvent combinations can be easily compared. The NCE of the characteristic solvents tested appear in Table 5.1.

Table 5.1 – Experimental NCE of fluorous-tagged phosphine oxide in characteristic solvents.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>NCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>&gt;200</td>
</tr>
<tr>
<td>DMSO</td>
<td>37</td>
</tr>
<tr>
<td>Methanol</td>
<td>1.5</td>
</tr>
<tr>
<td>Hexanol</td>
<td>6.5</td>
</tr>
<tr>
<td>Heptane</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

The degree of retention fit qualitatively with what is known for fluorophilic solvents; fluorophobic solvents that were either very polar, such as water and DMSO, or very nonpolar, such as heptane, showed excellent retention (Figure 5.8). Fluorophilic solvents of middling polarity, methanol and hexanol, showed poor retention\(^{225}\). These experiments demonstrated that a fluorous-tagged catalyst could be immobilized for long periods of time if either a very polar solvent or very nonpolar solvent were used. As the tracer was 46 wt% fluorine, increasing the amount of fluorine was identified as one technique to increase retention strength.
5.5 Catalyst loading procedure

A technique for loading the catalyst onto the support needed to be developed. One technique would be to dissolve a known amount of catalyst in a volatile solvent, such as THF, add the fluorous silica gel, and after a period of agitation, remove the solvent by evaporation. A similar technique has been applied for fluorous catalyst recovery, where a solid fluorous sorbent has been added to a homogeneous solution.\textsuperscript{226,227}

While \textit{a priori} loading would have the advantage of knowing the exact catalyst concentration on the support, the loading process would be time consuming, and could entail frequent loading and unloading of particles. Furthermore, some material would likely be lost during each loading and unloading application.

A more attractive technique would be to flow a solution of the catalyst across the bed. In this manner, the same support could be used for multiple catalysts, and the catalyst could be recovered after use by simply washing the bed. Loading in flow was thus investigated, knowing that the pre-weighing material was a feasible and safe back up plan.

Fortunately, loading in flow proved successful, and \textit{a priori} loading was not necessary. A typical loading procedure involved dissolving the fluorous catalyst in anhydrous tetrahydrofuran...
(THF) or toluene and passing the solution across the bed. The bed was allowed to rest for some time, normally 10-20 minutes, to enable diffusion of the catalyst across the surface, after which a large excess of dry heptane (3-5 mL) was rapidly passed over the bed until the eluting solvent was visually colorless. Typically no color was observed after 1 mL of heptane was passed across the bed. After washing with heptane, pressurized $N_2$ (30 psi) was used to dry the bed. The total loading procedure took roughly 45 minutes but could be streamlined by eliminating the heptane wash and drying step.

To characterize the amount of catalyst that could be retained, 14 mg (10 $\mu$mol) of a fluorous tagged salen catalyst in 400 $\mu$L THF was loaded using the above technique. More details about this catalyst appear in section 5.7 of this thesis. The catalyst was removed by washing the bed with 7.5 mL THF at 40°C. After drying, visual inspection revealed the lower portion of the bed retained material, so an additional wash of 7.5 mL THF was passed over the bed at 40°C, which resulted in a uniform white bed. Photographs from this process appear in Figure 5.9. The slight delineation in color in the middle of the bed is an artifact from the lighting in the room.

![Figure 5.9 - Catalyst loading technique using flow. From top to bottom: a) blank fluorous silica gel bed, 54 $\mu$L void volume, b) After passing 10 $\mu$mol of 0.025 M of the fluorous salen catalyst in THF over the bed, 5 mL of heptane, and then drying with $N_2$, c) After washing the bed with 7.5 mL THF at 40°C, and d) after washing the bed with a total of 15 mL THF at 40°C.](image)

The heptane wash and residual THF from the loading process were removed using a rotary evaporator, which resulted in a recovery of 6 mg of catalyst. Similarly, removal by evaporation of the THF from the wash process resulted in recovery of 7 mg of catalyst, which indicates the material balance on the catalyst closed within measurement error. The molar loading of the
catalyst was calculated as ~0.05 mmol catalyst per gram of fluorous silica gel, which is slightly lower than other silica supported catalysts with loadings ranging from 0.17 to 0.65 mmol/gram support\textsuperscript{23}.

### 5.6 Fluorous silica gel characterization

Fluorous-silica gel (FSG) (FluorouFlash\textsuperscript{TM} Silica Gel, Fluorous Technologies Inc.) used in this study was received as a donation from Fluorous Technologies Inc. The silica gel was reported to have physical properties described in Table 5.2.

<table>
<thead>
<tr>
<th>Table 5.2 – Reported physical properties of FluoroFlash Silica Gel.</th>
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</thead>
<tbody>
<tr>
<td><strong>Min</strong></td>
</tr>
<tr>
<td>Average pore size (Å)</td>
</tr>
<tr>
<td>Surface area (m\textsuperscript{2}/g)</td>
</tr>
<tr>
<td>Pore volume (cm\textsuperscript{3}/g)</td>
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<tr>
<td>Bulk density (g/cm\textsuperscript{3})</td>
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<tr>
<td>Organic loading</td>
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The organic loading wt\% was measured at 27\% separately using thermogravimetric analysis, which is within experimental error of the reported value. The supported fluorous chains came off primarily in the 500–600°C range. As a second measurement of catalyst loading, material prepared from loading using the flow technique was compared to a calibration curve created at different loadings (Figure 5.10). The major weight loss of the fluorous salen catalyst occurred at 300°C. The catalyst wt\% after loading by flow was found to be 5.2\%, which corresponds to a molar loading of 0.04 mmol catalyst/g FSG. This value is in good agreement to the loading obtained during the catalyst recovery experiment.
Figure 5.10 – Thermogravimetric analysis of fluorous silica gel technique with different catalyst loadings. Left: Wt% vs temperature. Right: Differential weight change as a function of temperature.

The particle size distribution of the fluorous silica gel was measured using both a coulter counter and laser diffraction. Coulter counter analysis works on the basis of electrical impedance as a particle passes through a constricted orifice. The reported particle size is for a solid sphere of equal mass and neglects internal porosity. Suspended FSG particles in ethanol were measured using a Coulter counter in the Langer lab at MIT with a mean particle size of 59.6 ± 9.6 micron. Conversely, measurements with an optical technique, such as laser diffraction, provide an estimate of the actual size. The particle size distribution measured using a Malvern Mastersizer 2000 instrument resulted in a broader and larger distribution, with a mean particle size of 81 ± 22 micron (Figure 5.11). Comparisons of these distributions allowed an estimate of an average internal porosity, $\varepsilon$, of 54% using equation 5.4. Both results fit a normal distribution quite well (equation 5.5).
Figure 5.11 – Comparison of particle size distribution measurements of FSG using a Coulter counter and laser diffraction.

$$\varepsilon = \frac{V_{LD} - V_{CC}}{V_{LD}} = 1 - \frac{d_{p,CC}^3}{d_{p,LD}^3}$$

(5.4)

$$Vol\% = \sqrt{\frac{1}{2\pi\sigma^2}} \exp \left[ -\frac{(d_p - \bar{d}_p)^2}{2\sigma^2} \right]$$

(5.5)

Separately the void volume of a packed reactor was measured to be 74% using inline UV measurements. These experiments are described in chapter 2 of this thesis. With a solids volume of 34 μL in a 130 μL reactor after packing and an internal porosity of 54%, the packing efficiency could be calculated using equation 5.6 and was determined to be 48%, which is a reasonable value for a bed of randomly packed spheres but indicates some compression may be achievable, as the maximum theoretical packing efficiency for irregular packing is ~64%.

$$\eta_{packing} = \frac{V_{solid}}{\varepsilon V_{Tot}}$$

(5.6)

5.7 Fluorous-tagged Co(III)-Salen catalysts

Use of fluorous-tagged Co(III)-salen catalysts (MW: 1440, 48 wt% fluorine) have previously been used to effect the catalytic ring opening of 1,2-epoxyhexane with a stoichiometric amount of water (Figure 5.12). The catalyst showed good performance compared
to the standard salen catalyst and was successfully recycled using a phase selective extraction, though multiple extractions were not attempted\textsuperscript{230, 231}. As epoxyhexane closely resembles heptane in terms of structure, and retention of the fluorous phosphine oxide was excellent in both water and heptane, this reaction was selected as a candidate reaction for flow conditions.

![Image of racemic fluorous salen(III) catalyst](image)

**Figure 5.12 – Racemic fluorous salen(III) catalyst.**

Initial experiments were performed using 0.07 M epoxyhexane in heptane with a 1:1 volumetric flow rate of water using a racemic catalyst (Figure 5.13). A large excess of water was thus present in the reactor. These conditions are in contrast to the standard conditions developed by Jacobsen and coworkers, which use a chiral catalyst to effect enantioselective ring opening of the epoxide and run the reaction neat with 0.7 equivalents of water\textsuperscript{232, 233}. The racemic Co(II) fluorous catalyst was readily available from Fluorous Technologies, Inc., and was provided as a donation. Oxidation to the catalytically active Co(III)-salen catalyst was accomplished by adding a stoichiometric amount of trifluoroacetic acid to the dissolved salen complex. DMSO in the aqueous phase and dodecane in the organic phase served as internal standards. Flowrates were controlled by Harvard PhD 2000 syringe pumps, and the aqueous and organic streams first met off chip using a PEEK T to create segmented flow. Collection of samples was performed off chip after dilution of each phase by additional heptane and deionized water. Analysis of the organic phase, which was manually separated using a Pasteur pipette, was performed by gas chromatography (GC). Conversion was measured by disappearance of the starting material relative to the internal standards.
Figure 5.13 – Ring opening of epoxyhexane with water in the presence of Co-salen(III) catalysts.

Initial stability studies were performed by flowing 20 μL/min total of 0.07 M heptane and water (10 μL/min per syringe) through a 8 mm wide bed (108 uL), which corresponds to a 5.4 minute residence time. Samples were collected and analyzed every 5 residence times. Conversion remained constant at 73% for 40 residence times, so the experiment was continued overnight. A sample after approximately 200 residence times showed no change in conversion.

To confirm that the physically adsorbed material was responsible for the ring opening, control experiments using just fluorous silica gel under identical flow conditions was performed; no conversion was demonstrated even upon increasing the residence time to 10 minutes. A homogeneous batch experiment using the same amount of catalyst also showed significantly reduced conversion relative to the flow system after 5 minutes. From this experiment we concluded the epoxide opening was due to the physically adsorbed catalyst and the high conversion obtained was a result of the high concentration of catalyst within the packed bed. Estimation of the retained catalyst showed the molar loading to substrate ratio within the packed bed reactor was approximately 100 mol%. Conversely, a typical batch protocol for this reaction would use 0.15 mol% catalyst and require 3 hours\(^{233}\) (average TOF of 1.8 min\(^{-1}\), assuming use of enantioselective catalyst). This experiment was performed before optimizing the catalyst loading procedure, and loading of the fluorous catalyst for these experiments was estimated to be only 2 μmol on 100 mg FSG.\(^{234}\) Over 200 residence times at 73% conversion, a total of 1.02 mmol of epoxyhexane were opened, which corresponds to a TON of 510 and a TOF of 0.5 min\(^{-1}\).

Without reloading the bed, the activity of the adsorbed catalyst was investigated by varying residence time and temperature. Residence times from 30 seconds to 10 minutes were
investigated, and the temperature was varied from 25°C to 55°C. At 25°C, 93% conversion was obtained after 10 minutes. At 55°C, 97% conversion was obtained in 2.5 minutes and no starting material was detected after 5 minutes. This data appears in Figure 5.14.

![Figure 5.14 - Fluorous salen stability (left) and activity (right) plots for the ring opening of epoxyhexane (0.07 M) in heptane.](image)

The excellent stability and activity prompted investigation of conditions more similar to those used by Jacobsen$^{233}$. The effect of increasing the concentration of epoxyhexane to 1 M while maintaining an equal volume of water was investigated. Initial conversion was similar to that of the conditions at 0.07 M; however, the eluent had a slight yellow tint reminiscent of the dissolved catalyst species (Figure 5.15).

![Figure 5.15 - Comparison of conversion between 0.07 M and 1.0 M feeds of epoxyhexane.](image)
Stability experiments at a 5 minute residence time were performed. After ~50 residence times, the bed was dried with nitrogen and visually inspected, which revealed loss of color in the top portion of the bed. The experiment was allowed to continue for three days with intermittent sample analysis. After a period of initial stable activity, conversion decreased nearly linearly with time from 83% to <25% (Figure 5.16). The linear decrease and colored eluent indicated the catalyst was eluting from the bed and was not deactivating. As the choice of solvent was found to have a strong effect on retention of the fluorous phosphine oxide tracer, reduced retention when the solvent polarity is increased due to higher concentrations of the diol product was not surprising.

Figure 5.16 – Long term catalyst stability study using 1.0 M epoxyhexane in water. Left: Conversion as a number of residence times. Right: Photograph of bed after 50 residence times.

The results from the initial study with the racemic catalyst prompted us to investigate whether enantioselective ring openings could be achieved. Using the material synthesized by the researchers at the Broad Institute, enantiomeric excess (ee) of only ~70% were achieved at high conversions, and the reproducibility of these results was quite poor. As this chemistry was only intended as a proof of concept for the technique, no detailed investigation into the cause of the reduced ee was instigated.
5.8 Catalyst recycling using multiple beds in series†

To counteract the loss of activity at the higher substrate loading, a method for recycling temporarily immobilized catalysts was developed that involves at least two beds in series. The first bed is loaded with the physically absorbed catalyst and the second bed contains blank material. The catalyst is captured by the second bed after eluting from the first bed. Once substantially all of the catalyst has left the first bed and been captured on the second bed, the order of the beds are switched. The manner in which the beds rearrange resemble a simulated moving bed for continuous chromatographic separations. Two possible valving schemes were identified for this procedure. The simplest scheme involved a single 4-port 2-position valve, which enabled reversal of the flow direction under a closed loop arrangement (Figure 5.17); however, conversion from such a setup would be inconsistent, as material in the system when a switch occurred would see 0-200% of catalyst compared to normal operation. A more complicated scheme was developed to maintain flow through both beds in the same direction to surmount this problem.

† Themes from this section appear in US 20110189749/WO 2011091243.
Figure 5.17 – Catalyst recycling using two beds in series. Left: Initial design with flow reversal. Right: enhanced scheme to maintain constant catalyst exposure.

Figure 5.18 – Catalyst recycling using two beds and a 10-port 2-position valve. Top: Schematic with a single 10-port 2-position valves. Bottom: Photograph of setup.
The initial design required multiple three port valves; however, an improved design was found that only required a single 10-port 2-position valve (Figure 5.18). The experimental setup with the 10-port 2-position valve was tested using inline UV-Vis with pulse injections and manually activating the 2-position valve. Extended retention of the tracer (toluene in methanol) was observed; after a single switch 97% of the tracer was captured on the second bed.

After a second switch, 85% of the material was recaptured on the third (e.g. first) bed. However, peak broadening was also observed (Figure 5.19). While the proposed platform was found to extend catalyst retention, losses due to dispersion would prevent retention ad infinitum.

![Characterization of multiple beds in series for retaining material.](image)

### 5.9 Fluorous-tagged metathesis catalysts

Ruthenium mediated olefin metathesis has been applied to numerous reactions, such as ring closures, ring opening polymerization, cross metathesis, and asymmetric variations of the above\textsuperscript{237-240}. The development of the air and moisture stable Hoveyda-Grubbs precatalyst has led to facile protocols for studying these systems\textsuperscript{241}. These catalytic systems are highly active and are known to deactivate in solution\textsuperscript{242, 243}; a recent detailed mechanistic study concluded that Grubbs metathesis catalysts had the highest activity of any known catalyst to date\textsuperscript{244}. Given the inherent trade off of activity and stability in catalysts, perhaps it is not surprising that attempts to
immobilize metathesis catalysts on solid supports have met with limited success. Whether metathesis catalysts immobilized through physical adsorption would display the same deactivating behavior was of interest.

To study the behavior of fluorous-physisorption for metathesis catalysts under continuous flow conditions, a fluorous-tagged Hoveyda-Grubbs catalyst was synthesized by substitution of an equatorial chloride with a silver carboxylate salt in dichloromethane (Figure 5.20). Both the mono (34 wt% F) and bis (45 wt% F) substituted catalysts could be readily synthesized by controlling the number of equivalents of carboxylate salt (1 eq and 2 eq, respectively) and were very soluble in standard organic solvents.

![Figure 5.20 – Standard Hoveyda-Grubbs catalyst (far left) and fluorous-tagged Hoveyda-Grubbs metathesis catalysts.](image)

The ring closing metathesis reaction of N,N-diallyltosylamide (NTs) was chosen as a model reaction (Figure 5.21), and initial experiments with the mono substituted catalyst showed good activity, achieving 75% conversion in 10 minutes and complete conversion in 40 minutes at room temperature with 1 mol% catalyst. As the mono substituted catalyst was found to be more active than the bis substituted catalyst, the majority of the remaining experiments were carried out with the mono substituted catalyst.

![Figure 5.21 – Model ring closing metathesis reaction. An equivalent of ethylene is generated as a side product. Ts = p-toluenesulfonyl](image)
Typical reaction conditions were 0.2 M substrate in toluene using biphenyl as an internal standard. The reaction was quenched by addition of di(ethylene glycol) vinyl ether (DEGVE)\textsuperscript{246}, 10 molar equivalents, in methanol and was monitored by HPLC using an isocratic method (60:40 Methanol:Water) over a reverse phase column (Figure 5.22).

![Calibration curves for the metathesis reaction.](image)

**Figure 5.22 – Calibration curves for the metathesis reaction.**

Continuous flow experiments were performed in an analogous manner to the batch experiments. The catalyst was loaded by passing a solution of fluorous-tagged catalyst (5.2 mg) in toluene (0.4 mL) across the FSG bed. The reactor eluent was quenched by feeding directly into a vial containing DEGVE or later by introduction of DEGVE through a T. Unfortunately, initial continuous flow activity studies using the ring closing metathesis reaction of NTs, where residence time was varied by changing flow rate, showed evidence of loss of activity (Figure 5.23).

Loss of activity was verified when conversion was monitored at a two minute residence time. Notably use of chlorinated solvents, such as dichloroethane, resulted in significantly accelerated loss of activity, whereas use of either benzene or toluene showed nearly identical deactivation profiles. Initial operation of the bed showed a significant amount of gas formation, which passed out of the weir as bubbles but could also be seen on the bed as a lighter color. Visual inspection
of the bed throughout the reaction revealed that loss of activity proceeded from the front of the bed towards the exit due to the absence of gas (Figure 5.24).

![Bar chart showing conversion and yield over time](image)

**Figure 5.23 – Initial activity study of NTs.** Residence times are labeled above the bar chart. Comparison at 1 min showed clear loss of activity.

Conversion decreased from 100% to less than 50% after only 23 reactor volumes when using toluene as the solvent with a 2 minute residence time. As Grubbs has previously identified intermolecular decomposition as one of the primary catalyst deactivation pathways$^{242}$, and the bulk catalyst concentration in the microreactor system, 0.13 M, is two orders of magnitude higher than typical batch conditions, ~0.001 M, accelerated decomposition due to the higher catalyst concentration was possible. Considering physically adsorbed catalysts can diffuse across the surface of the support, the potential for intermolecular interactions was likely accelerated in this system. Elucidating whether deactivation or elution was responsible for the loss of activity was critical to understanding the feasibility of fluorous immobilization for metathesis catalyts.
Figure 5.24 – Stability study of NTs in different solvents at a two minute residence time. Left: Reaction plots. Right: Photographs of the bed at various time points.

Catalyst loading was varied from 1.2 mg to 7.2 mg for a 2 mm wide bed (28 μL) and was found to have little impact on the rate of deactivation. Loading above 5.2 mg was found to have no effect on conversion (Figure 5.25). The deactivation profiles were identical for all cases investigated.

Figure 5.25 – Effect of catalyst loading on conversion and deactivation profiles.

The use of a two reactors in series, where both reactors contained fluorous silica gel but only the first reactor was loaded with catalyst, was used to study this phenomenon. If the catalyst was simply eluting, a period of steady conversion should precede any loss in activity (Figure 5.26). The volume of the capture bed was roughly twice that of the bed loaded with catalyst to amplify
retention. The residence time was calculated based only on the volume of the reactor loaded with catalyst (28 μL) for both cases. Normalizing time zero to be when fluid first exits the reactor, the deactivation profiles between a single bed and two beds in series are almost identical, with only a very slight performance increase when using a second bed. Furthermore, ICP analysis of the eluent after loading and samples from the 2nd and 4th fractions verified that Ru levels were less than 2% of the initial loading solution concentration. Based on these results, deactivation, and not elution, was deemed to be the dominant mechanism for activity loss.

Several operating parameters were studied to determine whether deactivation could be mitigated. Ethylene concentration in solution was increased by applying 5 bar of back pressure, which completely eliminated the formation of a gas phase (Figure 5.27). As metathesis reactions are reversible, application of back pressure was expected and observed to reduce conversion due to...
to higher dissolved ethylene concentrations. The deactivation rate in both cases followed first order behavior with similar time scales.

![Figure 5.27 – Deactivation profiles under 5 psi and 75 back pressure. Left: Conversion vs. time. Right: Natural log of conversion vs. time.](image)

Conversely, application of a membrane reactor was employed to remove ethylene as it formed. This reactor used a modular separator chuck frequently used to perform liquid-liquid or gas-liquid separations. A Teflon AF membrane was used in place of the typical Zefluor PTFE membrane, and the permeate outlet from the chuck was connected to a vacuum pump. Fluorous silica gel was loaded into the chuck and retained using a stainless steel frit. No appreciable change in the time scale of deactivation was observed using the membrane reactor. These results indicate dissolved ethylene was not responsible for loss of activity in this system (Figure 5.28).
Figure 5.28 – Removal of ethylene did little to stem catalyst deactivation. Top left: Conversion vs. time. Top left: Natural log of conversion vs. time. Bottom: Membrane packed bed reactor schematic.

While deactivation was found not to be preventable, the results were comparable to those achieved by Ying and co-workers, who tested a covalently grafted metathesis catalyst on mesocellular foams (Figure 5.29)\textsuperscript{248}. The researchers found rapid deactivation when using toluene as the solvent; running the reactor in a differential fashion with large recycle resulted in reduced deactivation.
Figure 5.29 – Deactivation under flow conditions for a heterogeneously grafted metathesis catalyst from Lim et al\textsuperscript{248}. Left: Conversion vs. time. Right: Catalyst structure.

The fluorous platform was able to achieve the same behavior without covalent grafting while using 1/9\textsuperscript{th} the amount of catalyst. Molar loadings between the two platforms were comparable, and the fluorous tagged catalyst was simpler to synthesize. A comparison of the two platforms appears in Table 5.3. The fluorous platform was thus able to accurately capture the behavior of a traditional immobilization technique, covalent grafting, without requiring grafting.

Table 5.3 – Comparison of fluorous platform and covalently grafted catalyst platforms for studying immobilized methathesis catalysts.

<table>
<thead>
<tr>
<th></th>
<th>This work</th>
<th>Lim et al\textsuperscript{248}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat. wt (mg)</td>
<td>5.2</td>
<td>225</td>
</tr>
<tr>
<td>mmol cat</td>
<td>4.2</td>
<td>36</td>
</tr>
<tr>
<td>t/τ, 50% conversion</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>Loading (mmol/g support)</td>
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<td>0.16</td>
</tr>
<tr>
<td>Synthesis steps</td>
<td>1</td>
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Continuous regeneration of the deactivated catalyst by feeding dissolved catalyst with the substrate was found to result in stable, high conversions and yields. The mechanism behind the enhanced performance and summary of results appear in chapter 6 of this thesis.
5.10 Conclusions

A comprehensive investigation of the feasibility of fluorous physisorption as a catalyst immobilization technique has been performed. A simple packed bed microreactor was designed and fabricated while improving upon previous designs. Techniques for rapidly loading and unloading catalyst particles were developed, with loading dry particles using vacuum proving superior to loading a slurry.

Initial characterization studies of tracer retention demonstrated that solvent selection played an important role in retaining a fluorous-tagged phosphine oxide tracer. Both very polar and very non-polar solvents were found to retain the tracer for long periods of time, whereas fluorophilic solvents of middling polarity were found to show little retention. The ability to load a catalyst under flow conditions was demonstrated, with catalyst loadings close to 0.05 mmol/g support being demonstrated.

Investigation of a fluorous-tagged Co(III)-Salen catalyst showed excellent activity and stability at moderate concentrations. Both a kinetic and stability study on the ring opening of epoxyhexane were performed using a total of 12 mg catalyst at a concentration of 0.07 M substrate. Increasing the substrate concentration to 1.0 M resulted in linear decrease in conversion over a period of three days. The loss of activity was attributed to elution of the catalyst.

A technique for prolonging the lifetime of a physically adsorbed catalyst under flow conditions was developed. This technique used multiple beds in series and the ability to control the order of the beds to continuously recapture catalyst as it was eluted. Characterization of the system revealed the technique was able to retain 85% of the catalyst over three cycles, though diffusive losses would ultimately prevent infinite recycle.
A fluorous-tagged Hoveyda-Grubbs metathesis catalyst was characterized under both batch and continuous flow conditions. Loss of activity with time was observed, which was determined to be from deactivation and not elution by using multiple beds in series. Efforts to stem deactivation by removal of ethylene proved fruitless. The behavior of the physically adsorbed catalyst matched the behavior of a covalently grafted catalyst from literature. Comparison of the fluorous platform to the covalently grafted platform revealed the fluorous platform was advantageous in several categories. This result demonstrates the utility of physical adsorption techniques for correctly characterizing immobilized catalyst behavior.
6.1 Motivation

Liquid chromatography (LC) and high performance liquid chromatography (HPLC) systems are widely used to separate compounds on either a preparative or analytical scale\textsuperscript{249-253}. While numerous supports and solvents have been developed for specialized applications, in general, these systems rely on differences in interactions between the solutes and the solid phase to effect separation. Choice of solvent and solid phase can have a drastic effect on the retention time of solutes; specifically, compounds that interact more strongly with the solid phase have a longer retention time on the column. These separation techniques are typically used where a pulse of material is injected onto the column, and then pure fractions of material are quantified or isolated (Figure 6.1).

Figure 6.1 – Schematic of chromatographic separations with pulse inputs.

A common industrial separation technique related to chromatography involves the use of adsorption beds for the removal of contaminants from a product stream\textsuperscript{254-256}. A continuous feed stream enters the bed, and the contaminant adsorbs on the bed. Once a bed comes close to
saturation, the effluent concentration begins to rise and ultimately reaches the inlet concentration. At this point, the bed must be regenerated, which is frequently done using either thermal-swing\textsuperscript{257,258} or pressure-swing\textsuperscript{254,259}.

The application of adsorption techniques for continuous flow processes can lead to unique operational benefits compared to homogeneous flow or batch processes. An industrially relevant example involves use of simulated moving beds (SMB) for continuous chromatographic separations of organic molecules\textsuperscript{236, 260, 261}. SMB processes use complex arrays of adsorbent beds and adjust the physical feed, inlet, and eluent locations to obtain pure component streams. Both pulse\textsuperscript{262} and continuous injection\textsuperscript{263-265} of reagents onto adsorbent beds have been used to exceed equilibrium limits. This enhancement occurs due to a difference in retention of the substrate and product, which drives the reaction in the forward direction while enabling simultaneous purification.

The previous examples rely on simultaneous reaction and separation to exceed equilibrium; however, a steady-state mass balance around the bed reveals the concentration of adsorbed species under continuous inputs will exceed the feed concentration, which has interesting implications. For example, for the case where a feed stream comprising multiple species is injected onto a column with substantially different retentions, the ratio of concentrations on the column is different from the ratio in the feed stream. This difference in ratios can beneficially affect chemical kinetics for several reaction types.

In particular, homogeneous catalyzed reactions where the catalyst has increased affinity to the surface can be accelerated due to augmented catalyst concentration under the condition that the adsorption does not reduce the catalyst's activity. Similarly, reactions requiring excesses of a reagent can potentially be run using lower excess loadings. Furthermore, since the residence
time of the species in the bed can be increased relative to the bulk solvent retention time, reactor space time yields can potentially be increased by operating at higher concentrations in smaller reactor volumes. This technique could be broadly applicable and can be tailored to individual applications by using different solvents and packing material to change surface-solute interactions.

6.2 Mathematical treatment of selective adsorption processes

Adsorption onto a solid support under flow conditions is a complicated process involving several steps that involve mass transfer, chemical kinetics, and thermodynamics; a number of steps can be limiting\textsuperscript{266-268}. As adsorption sites can be located either on the external surface or in pores, either external or internal mass transfer to a site can be limiting. For the case of chemical adsorption, the rate of reaction of the solute with the adsorbent can be limiting. As many useful adsorption processes are reversible, thermodynamic equilibriums of the adsorption process must be favorable, and knowledge about the relationship between material adsorbed on a support and in solution must be taken into account. Furthermore, these processes are transient, which requires analysis using partial differential equations instead of ordinary differential equations. Successful modeling of an adsorption process requires sufficient knowledge about a particular system to make reasonable assumptions.

An ideal adsorption process would abide by the following restrictions: 1) plug flow at a constant velocity, 2) instantaneous equilibrium at the surface, and 3) isothermal operation\textsuperscript{256}. Breakthrough profiles under these conditions for the generic species $A$ can be described using equation 6.1, where $q$ represents the solid phase concentration of the adsorbed species, $A$ represents the liquid phase concentration of species $A$, and $\varepsilon_b$ is the overall bed porosity. This equation simplifies to the plug flow equation for a step change in concentration in the absence of
adsorption. The parameter $q$ can be related to equilibrium adsorption through equation 6.2^2^5^6, though different adsorption isotherms (e.g. linear, Langmuir, or BET) can affect the resulting behavior. The solution to this PDE describes the concentration wave front, $u_A$, in relationship to the bulk fluid velocity, $u$ (equation 6.3).

$$\frac{dA}{dt} = \frac{1 - \varepsilon_B}{\varepsilon_B} \frac{dq}{dt} - u \frac{dA}{dz}$$ \hspace{1cm} (6.1)

$$K = \frac{q}{A}$$ \hspace{1cm} (6.2)

$$u_A = \frac{u_{bulk}}{1 + \frac{1 - \varepsilon_B}{\varepsilon_B} \frac{dq}{dA}}$$ \hspace{1cm} (6.3)

As the denominator is always greater than or equal to one, the concentration wave front is slowed relative to the bulk fluid, and for linear isotherms or operation under linear adsorption conditions (equation 6.4), the wave front moves at a constant velocity (Figure 6.2). Defining the number of column equivalents ($NCE$) to be the ratio of the residence time of the solute to the bulk fluid (equation 6.5) assuming no compression of the adsorbent, the NCE for A is the denominator of equation 6.3 (equation 6.6).

$$\frac{dq}{dA} = \alpha$$ \hspace{1cm} (6.4)

$$NCE = \frac{\tau_A}{\tau_{bulk}} = \frac{u_{bulk}}{u_A}$$ \hspace{1cm} (6.5)

$$NCE_{A, ideal} = 1 + \frac{1 - \varepsilon_B}{\varepsilon_B} \frac{dq}{dA}$$ \hspace{1cm} (6.6)
Figure 6.2 – Schematic of concentration wave fronts under ideal adsorption conditions.

Should the system be allowed to operate past the point of complete saturation, which is never intentionally done when adsorption is used as a means to remove contaminants, a mass balance on the bed reveals $A$ is enhanced relative to the feed stream. The relationship of the feed concentration and bed concentration can be given as the product of the feed concentration and the NCE required for elution (equation 6.7). For the case where multiple species are fed through a bed, the ratio of the concentrations in the bed volume depends on the NCE of each species and the feed concentrations (equation 6.8).

$$A_{\text{reactor}} = \frac{A_{\text{feed}} NCE_A}{B_{\text{feed}} NCE_B}$$

Thus, should species $A$ selectively adsorb onto a support, the bulk concentration of $A$ in the reactor will be higher than the feed concentration (Figure 6.3). While the transient behavior of adsorption systems likely does not match the idealized behavior previously described, the steady state performance for a completely saturated bed described by equations 6.7-8 will hold regardless of the type of adsorption. Thus, experimentally measured NCEs provide sufficient information for analysis.
Figure 6.3 – Concentration enhancement of A relative to B when A adsorbs but B does not.

The underlying assumptions of the idealized adsorption model are likely not met in reality. The PDE describing adsorption when dispersion effects and mass transfer effects are considered is given by equation 6.9, where $D_e$ represents an effective diffusivity the last term is the volume averaged adsorption due to concentration gradients within a particle (equation 6.10)\textsuperscript{256, 266}.

\[
\frac{dA}{dt} = D_e \frac{d^2 A}{dz^2} - \frac{d(uA)}{dz} - \frac{1 - \varepsilon_B}{\varepsilon_B} \frac{d\bar{q}}{dt}
\]  
(6.9)

\[
\bar{q} = \frac{3}{R_p^3} \int_0^{R_p} qr^2 dr
\]  
(6.10)

The solution to equation 6.9 when dispersion is neglected and the mass transfer driving forces is assumed to be linear with concentration (equation 6.11) has the form of an error function with two dimensionless parameters, $\zeta$ and $\omega$, which correspond to scaled distance and time, respectively (equation 6.11-13). In equation 6.11, $k$ represents the overall mass transfer coefficient and includes internal and external resistance and $A^*$ is the equilibrium saturation concentration. This model has error <0.6% if the non-dimensional distance $\zeta$ is larger than 2.

\[
\frac{d\bar{q}}{dt} = kK \left( A - A^* \right)
\]  
(6.11)

\[
A(\omega, \zeta) = \frac{A_{\text{inlet}}}{2} \left[ 1 + \text{erf} \left( \sqrt{\omega - \sqrt{\zeta} + \frac{1}{8\sqrt{\omega}} + \frac{1}{8\sqrt{\zeta}}} \right) \right]
\]  
(6.12)

\[
\zeta = kK \frac{z}{u} \left( \frac{1 - \varepsilon_B}{\varepsilon_B} \right)
\]  
(6.13)

\[
\omega = k \left( t - \frac{z}{u} \right)
\]  
(6.14)
The form of equation 6.12 captures the experimentally observed mass transfer zone, which corresponds to a concentration gradient at the front of the wave due to diffusion and is sufficient for the present analysis. The combined effects of dispersion and diffusion are problematic for adsorption separation processes as it reduces capacity (Figure 6.4).

Figure 6.4 – Concentration wave fronts in adsorption reactors show accelerated breakthrough in the “mass transfer zone.”

As steady state behavior is of primary concern, complete saturation across the entire bed, which occurs when the coordinate $z$ is equal to the length of the bed, $L$, is of interest. This condition occurs when the second term in equation 6.12 equals unity (equation 6.15). As the value of the error function asymptotically approaches 1 and is 0.995 at when the argument is 2, further simplification of saturation conditions can be made (equation 6.16).

$$\text{erf} \left\{ \sqrt{\omega} - \sqrt{\zeta} + \frac{1}{8\sqrt{\omega}} + \frac{1}{8\sqrt{\zeta}} \right\} = 1 \quad (6.15)$$

$$\sqrt{\omega} - \sqrt{\zeta} + \frac{1}{8\sqrt{\omega}} + \frac{1}{8\sqrt{\zeta}} = 2 \quad (6.16)$$

If the non-dimensional time when saturation occurs at the outlet is greater than 2000 (equation 6.17), estimating $\zeta = \omega$ (equation 6.18) results in less than 10% error (Table 6.1). Rearrangement of this relationship results in a simple estimate of the equilibrium constant as a function of NCE and bed porosity (equation 6.19).
\[ \omega_i = k \left( t - \frac{L}{u} \right) = k \tau \left( t - 1 \right) = k \tau (NCE_i - 1) > 2000 \]  
(6.17)

\[ k \tau R (NCE - 1) = kK_i \tau R \left( \frac{1 - \varepsilon_B}{\varepsilon_B} \right) \]  
(6.18)

\[ K_i = \frac{\varepsilon_B (NCE_i - 1)}{1 - \varepsilon_B} \]  
(6.19)

Table 6.1 – Selected solutions to equation 6.16 and error from estimating \( \zeta = \omega \)

<table>
<thead>
<tr>
<th></th>
<th>( \zeta )</th>
<th>Error (%)</th>
<th>( \omega )</th>
<th>( \zeta )</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>65</td>
<td>55%</td>
<td>2500</td>
<td>2305</td>
<td>8%</td>
</tr>
<tr>
<td>200</td>
<td>148</td>
<td>35%</td>
<td>3000</td>
<td>2785</td>
<td>8%</td>
</tr>
<tr>
<td>500</td>
<td>415</td>
<td>20%</td>
<td>3500</td>
<td>3268</td>
<td>7%</td>
</tr>
<tr>
<td>1000</td>
<td>878</td>
<td>14%</td>
<td>4000</td>
<td>3752</td>
<td>7%</td>
</tr>
<tr>
<td>1500</td>
<td>1350</td>
<td>11%</td>
<td>4500</td>
<td>4236</td>
<td>6%</td>
</tr>
<tr>
<td>2000</td>
<td>1826</td>
<td>10%</td>
<td>5000</td>
<td>4722</td>
<td>6%</td>
</tr>
</tbody>
</table>

The solutions to equation 6.13-14 and 6.16 allow for an estimate of the equilibrium coefficient under flow conditions even if \( \omega_i < 2000 \) and rely mainly upon easily measurable parameters. These solutions should be applied to adsorption measurements and not desorption measurements, as desorbed material is continuously readsorbed along the length of the bed. The one parameter that must be either measured or estimated is the mass transfer coefficient of the species to the adsorption sites. Fortunately, correlations exist to predict mass transfer from bulk liquids to the surface of a packed bed and rely on an estimate of the Sherwood number\(^{153, 269, 270}\), \( Sh \), which corresponds to the ratio of convective mass transfer to diffusion (equation 6.20-21).

\[ Sh = \frac{k_e d_p}{D} \]  
(6.20)

\[ Sh = \frac{k_e d_p}{D} = 2 + 1.1 \left( \frac{d_p G}{\mu} \right)^{0.6} \left( \frac{\mu}{\rho D} \right)^{1/3} \]  
(6.21)

As the mass transfer coefficient in equations 6.20-21 have units of velocity, scaling the mass transfer by the diameter of the particle is necessary to achieve a mass transfer coefficient representative of the system and with the appropriate units of \( s^{-1} \) (equation 6.22).
Equilibrium constants can thus be calculated from easily measured physical parameters, an estimate of the mass transfer coefficient, and an experimental measurement of the number of column equivalents to saturate a bed.

6.3 Hoveyda-Grubbs ring closing metathesis example†

Whether the use of adsorption reactors could be applied to the ring closing metathesis (RCM) chemistry described in detail in section 5.9 of this thesis was investigated. Loss of activity for a fluorous-tagged Hoveyda-Grubbs catalyst immobilized on fluorous-silica gel (FSG) had been determined to be from deactivation and not elution (Figure 5.26).

To test whether continuous replenishment of deactivated metathesis catalysts was feasible, a deactivation experiment was performed where a constant stream of N,N-Diallyltosylamide (NTs) was fed to the reactor at 0.2 M at a residence time of 2 minutes, either as a solution of 0.2 M or by mixing an equivolume in flow of 0.4 M with 0.66 mM fluorous tagged Hoveyda-Grubbs catalyst (0.17 mol%). The system was switched after 35 residence times from the 0.2 M solution to the 0.4 M + catalyst feed, back to the 0.2 M solution after a total of 60 residence times, and finally back to the 0.4 M NTs + catalyst at 95 residence times. The conversion decreased in accordance with previous results during the first portion of the experiment, leveled off at close to 60% conversion with continuous input of catalysts, decreased again after catalyst feed was stopped, and then increased and leveled off close to 60% conversion with continuous input of catalysts. This behavior indicated the catalyst could be replenished on the bed (Figure 6.5).

† The fluorous-tagged metathesis catalysts used in this section were prepared by Dr. Damian W. Young and co-workers at the Broad Institute.
To further investigate this, the catalyst (0.0066 M) and NTs solutions (0.4 M) were fed into two beds in series (28 μL followed by 56 μL) containing blank fluorous silica gel at equal volumetric flow rates, and conversion was monitored as a function of residence time. The bulk residence time of the liquids through both reactors without gas formation was close to 7 minutes. However, the formation of ethylene gas resulted in a reduced residence time. The actual residence time was estimated to be 5 minutes based on estimates of the solubility of ethylene in toluene at the reaction conditions\(^{271}\). The conversion reached 56% almost instantly and gradually decreased to about 48% over the course of the experiment, which corresponds to a steady state TON of ~300 and a TOF close to 60 min\(^{-1}\). The effects of the beds was investigated by repeating this experiment at room temperature with (1) both reactors initially empty, (2) the first reactor (28 μL) filled with fluorous silica gel and the second empty, (3) the same conditions in (2) but heating the first reactor to 40°C, and 4) filling both reactors with fluorous silica gel. These experiments were run sequentially using the same catalyst and NTs solutions. Almost no conversion was detected for (1), and reduced conversions were obtained under (2) and (3); use of both beds in series was found to be necessary to achieve the conversions from the previous experiment (Figure 6.6). The latter result indicates some reaction was occurring in the second

Figure 6.5 – Conversion of NTs using a fluorous tagged catalyst with periodic feed streams of homogeneous catalyst.

![Conversion graph](image_url)
bed, which implies leaching was also partially responsible for loss of activity in this system. This behavior is not inconsistent with the previous conclusion that deactivation was the primary vehicle for loss of activity, as the amount of time the catalyst was exposed to substrate in these examples was significantly lower compared to the multiple beds in series experiments described in chapter 5.

Further optimization of the process resulted in significantly enhanced TONs compared immobilization without co-flow. Summarized results and comparisons between the mono-substituted fluorous catalyst, bis-substituted fluorous catalyst, and standard catalyst (Figure 5.20) appear in Table 6.2. The residence time was calculated based on liquid feed rates and is an overestimate of the actual residence time due to gas formation. Starting material and product degradation was observed if the operating temperature was $>60^\circ$C. TOFs $>40$ min$^{-1}$ were obtained under with 0.2 mol% catalyst while achieving moderate conversions.
Table 6.2 – Comparison of catalyst performance under continuous flow selective adsorption. Conversions and yields were measured using HPLC. Highlighted rows can be directly compared.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>$T$ ($^\circ$C)</th>
<th>$\tau$ (min)</th>
<th>Catalyst</th>
<th>TON</th>
<th>TOF (min$^{-1}$)</th>
<th>Conv (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis fluorous</td>
<td>20</td>
<td>2.1</td>
<td>0.50%</td>
<td>52</td>
<td>25</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Bis fluorous</td>
<td>20</td>
<td>8.2</td>
<td>0.50%</td>
<td>85</td>
<td>10</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Bis fluorous</td>
<td>40</td>
<td>8.2</td>
<td>0.50%</td>
<td>172</td>
<td>21</td>
<td>86</td>
<td>71</td>
</tr>
<tr>
<td>Bis fluorous</td>
<td>60</td>
<td>8.2</td>
<td>0.50%</td>
<td>180</td>
<td>22</td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td>Bis fluorous</td>
<td>80</td>
<td>8.2</td>
<td>0.50%</td>
<td>184</td>
<td>22</td>
<td>92</td>
<td>64</td>
</tr>
<tr>
<td>Mono fluorous</td>
<td>22</td>
<td>2.1</td>
<td>0.50%</td>
<td>35</td>
<td>17</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Mono fluorous</td>
<td>22</td>
<td>8.2</td>
<td>0.50%</td>
<td>86</td>
<td>11</td>
<td>43</td>
<td>35</td>
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<tr>
<td>Mono fluorous</td>
<td>40</td>
<td>8.2</td>
<td>0.50%</td>
<td>154</td>
<td>19</td>
<td>77</td>
<td>72</td>
</tr>
<tr>
<td>Mono fluorous</td>
<td>60</td>
<td>8.2</td>
<td>0.50%</td>
<td>168</td>
<td>21</td>
<td>84</td>
<td>65</td>
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<tr>
<td>Mono fluorous</td>
<td>60</td>
<td>8.2</td>
<td>0.20%</td>
<td>358</td>
<td>44</td>
<td>72</td>
<td>55</td>
</tr>
<tr>
<td>Mono fluorous</td>
<td>80</td>
<td>8.2</td>
<td>0.20%</td>
<td>360</td>
<td>44</td>
<td>72</td>
<td>55</td>
</tr>
<tr>
<td>Mono fluorous</td>
<td>90</td>
<td>8.2</td>
<td>0.20%</td>
<td>388</td>
<td>47</td>
<td>78</td>
<td>64</td>
</tr>
<tr>
<td>Standard</td>
<td>20</td>
<td>4.1</td>
<td>0.50%</td>
<td>106</td>
<td>26</td>
<td>53</td>
<td>37</td>
</tr>
<tr>
<td>Standard</td>
<td>40</td>
<td>8.2</td>
<td>0.50%</td>
<td>159</td>
<td>19</td>
<td>80</td>
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<tr>
<td>Standard</td>
<td>40</td>
<td>8.2</td>
<td>0.50%</td>
<td>166</td>
<td>20</td>
<td>83</td>
<td>68</td>
</tr>
<tr>
<td>Standard</td>
<td>40</td>
<td>8.2</td>
<td>0.50%</td>
<td>170</td>
<td>21</td>
<td>85</td>
<td>70</td>
</tr>
<tr>
<td>Standard</td>
<td>60</td>
<td>8.2</td>
<td>0.50%</td>
<td>180</td>
<td>22</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>Standard</td>
<td>80</td>
<td>8.2</td>
<td>0.50%</td>
<td>188</td>
<td>23</td>
<td>94</td>
<td>57</td>
</tr>
</tbody>
</table>

Notably not much improvement was found using either fluorous catalyst compared to the standard catalyst when directly compared to each other. In order to investigate this unexpected result, breakthrough curve measurements of the standard Hoveyda-Grubbs catalyst dissolved in toluene were performed using the inline UV-Vis platform described in chapter 2 of this thesis. Light intensity was captured between 365-390 nm with a bulk fluid residence time of 4 minutes. No difference in the breakthrough curves was observed for the fluorous and non-fluorous metathesis catalysts using stainless steel beads as the packing (Figure 6.7). A slight hysteresis was observed, which was likely caused by compliance in the syringe when switching from the catalyst solution to the blank solvent.
Figure 6.7 – Breakthrough curves of the standard Hoveyda-Grubbs catalyst (HGL0) and monfluorinated Hoveyda-Grubbs catalyst (HGL1) through a packed bed of stainless steel beads show no evidence of retention. The hysteresis in the curves is likely due to an artifact from the pump.

Conversely, adsorption of the standard catalyst on fluorous silca gel was found to occur. Full adsorption took 5 column equivalents, whereas complete desorption took nearly 20 column equivalents (Figure 6.8). No discernable difference between the breakthrough curves at 20°C and at 60°C was observed which indicates the adsorption effect was not strongly affected by temperature in this case. With a bulk fluid residence time of 4 minutes, the mass transfer coefficient was estimated to be 0.5 s⁻¹ using equation 6.20-22. Under these conditions with a void fraction of 0.5, the absorption equilibrium constant $K$ for an NCE of 5 using equations 6.14-16 corresponds to 9.9. This unexpected adsorption of the standard catalyst on the fluorous support explains why no significant difference between the standard catalyst and fluorous-tagged catalyst was observed, as concurrent deactivation masked the effect of catalyst buildup in the fluorous bed.
Similar breakthrough curves experiments were performed on the tosylamide. As the UV-vis platform could not distinguish between the tosylamide and toluene, inline FT-IR using a Mettler Toledo flow cell was used to perform the measurement. Sufficient resolution was obtained by monitoring 928 cm\(^{-1}\), 1164 cm\(^{-1}\), or 1353 cm\(^{-1}\) wave numbers. For this experiment, the shift in residence time between replacing a union with a packed bed of fluorous silica gel was calculated to be within 1% of void volume of the bed, which indicates the substrate did not adsorb onto the support (Figure 6.9).
6.4 Lewis acid catalyzed Diels-Alder example

A second application of continuous flow selective adsorption reactors is the Diels Alder annulation of cyclohexadiene (CH) with methyl vinyl ketone (MVK) in 1,2-dichloroethane (DCE) using a perfluorinated scandium catalyst (Figure 6.10). The catalyst was synthesized according to literature procedures and involved the condensation of perfluorococanesulfonate with scandium trichloride in water to yield the catalyst as a white solid (MW: 1542, 63 wt% F)\(^{272}\). The solid catalyst could then be dissolved in tetrahydrofuran (THF) and distributed evenly over fluorous silica gel by slow evaporation of the solvent to yield the immobilized catalyst.

![Diagram](attachment:image.png)

Figure 6.10 – Scandium catalyzed Diels Alder annulation of cyclohexadiene and methyl vinyl ketone.

Batch recycling studies with a catalyst loading of 0.055 mmol/g at room temperature gave reasonable results, with GC yield decreasing from 81 to 75% after three cycles and a further decrease to 57% after five cycles, although GC yield ranged from 75-84% for all five cycles after 60 minutes. Letting the reaction run for longer times did not result in further increases in yield, which indicates the reaction had reached an equilibrium limit. The concentration of both CH and MVK after mixing was 0.45 M, and yield was monitored by GC using dodecane as an internal standard (Figure 6.11).

\(^\dagger\) Catalyst preparation was performed by Dr. Adam Sniady. Experimental results in this section were performed in collaboration with Dr. Damien Webb. Both Dr. Sniady and Dr. Webb were post-doctoral researchers in the Jamison lab at the time of this work.
Figure 6.11 – GC calibration curve of the product and dodecane. The relative response factor was 2.24 at equal concentrations.

The catalyst was tested under flow conditions using a 130 μL void volume microreactor at 20°C and at a total flow rate of 10 μL/min (τ = 13 minutes). Initial activity was excellent and matched the yield from the initial batch studies; however, allowing the reaction to proceed for 24 hours (144 residence times) resulted in a decrease in yield from 83% to <30%. The study was repeated with a five minute residence time, and the yield decreased from 65% to 20% over 60 residence times (Figure 6.12).

Figure 6.12 – Deactivation studies at τ = 10 minutes (left) and τ = 5 minutes (right).

The deactivation mechanism was further probed by addition of capture material to the system. A plug of fluorous silica gel supported catalyst was loaded at the top of a bed of blank fluorous silica gel (1:16 catalytic material:blank material by volume), and the deactivation
experiment was repeated. No deactivation was observed for 16 hours, and the rate of deactivation was reduced; GC yield decreased from 75% to only 45% over 32 hours after the initial period of initial stability. The period of relatively stable conversion before deactivation was strong evidence that activity loss was due to elution and not deactivation (Figure 6.13).

As elution was thought to be the dominant cause of activity loss, introduction of a continuous stream of catalyst was investigated. As the catalyst was extremely soluble in THF but almost completely insoluble in DCE, use of 30:70 THF:DCE v/v mixture was found to dissolve the catalyst at 6 mM (9 mg catalyst/mL solution), which was sufficient for further testing. Maintaining the vol% of THF as low as possible was desirable to prevent unwanted elution due to a more fluorophilic solvent environment. Mixing the reagent streams at a flow rate of 4.32 μL/min per reagent with the catalyst stream at a flow rate of 2.16 μL/min resulted in volumetric ratio of DCE:THF of 94:6 and resulted in a homogeneous catalyst feed ratio of 0.8 mol%.

![Figure 6.13 - Deactivation studies with 16 volumetric equivalents of blank fluorous silica gel to capture eluted catalyst.](image)

The catalyst feed stream and reagent streams were mixed using a silicon micromixer and fed to a packed bed containing either stainless steel beads or fluorous silica gel. Use of reactors filled with stainless steel bead resulted in <2% yield; conversely, use of fluorous silica gel resulted in an increase in yield from 2% to 42% over 25 residence times. The increase in yield
was due to accumulation of the catalyst material on the column; the equilibrium constant $K$ of the catalyst was calculated to be 78 with an NCE of 25 using equations 6.14-16. These results are the first successful augmentation of a catalytic process under continuous flow conditions due to selective adsorption of the catalyst (Figure 6.14).

Figure 6.14 – Increasing yield as a function of time due to accumulation of the catalyst within the reactor.

Further conditions were examined to see whether the equilibrium limit could be obtained, and a 10 minute residence time at 40°C was found to give 85% yield. This result represented a 12x increase in turnover frequency compared to the batch experiments (Table 6.3). An important note is that increasing the homogeneous catalyst loading beyond 1% was likely not possible due to the very limited solubility of the catalyst.

<table>
<thead>
<tr>
<th>Table 6.3 – Comparison of selective adsorption and batch results.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Batch</td>
</tr>
<tr>
<td>Yield</td>
</tr>
<tr>
<td>Time (min)</td>
</tr>
<tr>
<td>Catalyst</td>
</tr>
<tr>
<td>TOF (min⁻¹)</td>
</tr>
</tbody>
</table>
6.5 Series-parallel and equilibrium applications

A recent example of a series-parallel reaction under continuous flow conditions is the epoxide aminolysis of styrene oxide with 2-aminoindane\textsuperscript{82, 84}. The desired product, a β-amino alcohol, can further react with a second equivalent of epoxide to generate an undesired side product. Optimized processing conditions to minimize bisalkylation product formation required three equivalents of the amine. An example of an equilibrium limited reaction is a carboxylic acid-promoted lactone aminolysis reaction\textsuperscript{273}. Yield of the desired product was heavily dependent on the number of equivalents of amine; use of five equivalents of amine at 120°C resulted in 84% yield, whereas use of 20 equivalents resulted in 93% yield. While not done in either example, recycling the excess amine could reduce material costs in production settings.

Both series-parallel (equation 6.23-24) and equilibrium limited reactions (equation 6.25), as illustrated by the previous examples, are typically driven towards the desired product by addition of excess equivalents of one reagent to both improve selectivity and accelerate the reaction. MATLAB simulations for a generic series-parallel (Figure 6.15) and equilibrium reaction (Figure 6.16) further demonstrate these processing considerations.

\begin{align}
A + B & \xrightarrow{k_1} R \quad (6.23) \\
R + B & \xrightarrow{k_1} S \quad (6.24) \\
A + B & \xleftarrow{k_1} C \quad (6.25)
\end{align}
Application of a continuous flow selective adsorption reactor would have beneficial effects for both of these processes by reducing the feed ratios. An idealized continuous flow selective adsorption reactor could replace recycle loops in a system by augmenting the concentration of one species within the reactor. A comparison of a traditional recycle scheme with ideal
separation (e.g., the product and unreacted starting material are completely separated) and an ideal continuous flow selective adsorption reactor appear in (Figure 6.17). Both systems have the same feed composition, but the selective adsorption reactor would not require separations or recycle loops.

![Diagram of traditional recycle loop and selective adsorption reactor](image)

**Figure 6.17** – Comparison of traditional recycle loop (top) and selective adsorption reactor (bottom) for the model series parallel reactions described by equation 6.23 and Figure 6.16. The requirement for the selective adsorption reactor to perform in the manner described is $A_{bed}/B_{bed} = 5$.

### 6.6 Potential limitations of adsorption reactors

Some care must be taken to avoid potential problems when implementing a selective adsorption reactor. While the NCE of a solute may be experimentally measured, altering the feed concentration from the measurement can affect the retention if the adsorption isotherm is not linear. This concept can be thought of as “overloading a column,” which can result in reduced retention and occurs when the solute concentration is too high. A similar problem can arise if the retained solute concentration exceeds the solubility limit, which would likely result in precipitation and clogging. Thus, feed conditions may need to be more dilute than under homogeneous conditions.

The manner in which adsorption occurs can affect reactivity, particularly if the adsorption occurs near the reactive site of the molecule. For example, aromatic amines would likely adsorb to the hydroxyl groups on silica gel via hydrogen bonding, which might inhibit the reactivity of
the amine site. While care should be taken when selecting a sorbent, this effect does not preclude the use of selective adsorption reactors for these applications. If the product of the fraction of available molecules to react of species $i$ (equation 6.26), $F_i$, and NCE$_i$ is greater than one, the concentration of useful molecules within a reactor is enhanced relative to the feed stream, and use of selective adsorption reactor technology would be beneficial (equation 6.27)

$$F_i = \frac{\text{molecules of } i \text{ available for reaction}}{\text{total molecules of } i}$$  \hspace{1cm} (6.26)

$$NCE_i F_i > 1$$ \hspace{1cm} (6.27)

Also worth consideration for the case of series-parallel and equilibrium reactions is the adsorption of the product. If the desired product (R or C) shows an affinity for the support, the potential for further acceleration of the undesired reaction can occur. Thus, transformations that consume the functional group causing retention are ideally suited candidates.

### 6.7 Conclusions

A new reactor type, the continuous flow selective adsorption reactor, has been demonstrated to enhance catalytic reactions with continuous inputs of a homogeneous catalyst. These reactors augment the concentration of a physically adsorbed species relative to the feed concentration. These reactors behave mathematically in the same manner that adsorption columns for purifications work and can be modeled using the same equations. Furthermore, the ability to extract equilibrium adsorption constants using breakthrough curves was derived.

Application of the technique to a fluorous-tagged Hoveyda-Grubbs catalyst resulted in stable throughputs with significantly improved TONs and TOFs compared to previous experiments where the catalyst was only loaded at the beginning of the experiment. A competing effect, catalyst deactivation, masked the build up of catalyst on the bed and resulted in identical performance with the standard catalyst; furthermore, breakthrough curve measurements of the
standard catalyst revealed the surprising result that the standard catalyst was adsorbing on the fluorous silica gel.

The first successful demonstration of this reactor type for augmenting a catalytic application was achieved on a Diels-Alder reaction with a perfluorinated scandium catalyst. Introduction of the catalyst into a bed of fluorous silica gel resulted in a gradual build-up of yield, with steady state performance of 42% being achieved after 25 NCEs. The homogeneous reaction without the fluorous sorbent under identical conditions resulted in <2% yield. The equilibrium limited yield of 85% was obtained by increasing the bulk fluid residence time to 10 minutes and heating the flow reactor to 40°C. This result represented an order of magnitude improvement in turnover frequency compared to batch conditions.

Continuous flow selective adsorption reactors were also theorized to be applicable to homogeneous series-parallel and equilibrium reactors. Expectations that these applications will demonstrate enhanced performance should be tempered by understanding the potential limitations of the technology. For systems where an appropriate adsorbent can be identified, this technology offers unique advantages for flow systems that have not previously been exploited.
Ch 7. Conclusions and Outlook

7.1 Summary of thesis contributions

The major goal of this thesis was to expand and evaluate processing techniques for immobilized catalyst systems relevant to continuous flow. Due to the numerous benefits associated with studying chemical processes at small length scales, microfluidic devices were the tool of choice for most of the studies in this thesis. The first portion of the thesis demonstrated fundamental studies in residence time distributions, dispersion, and mixing. The second half of the thesis examined the feasibility of thermomorphic processes and physical adsorption techniques as immobilization techniques under flow conditions.

In chapter two, inline UV-vis spectroscopy was demonstrated as a technique for characterizing flow platforms. The platform was used to perform residence time distribution measurements for single liquid phase flow, liquid-liquid multi-phase flow, and gas-liquid multi-phase flow. Being modular, the platform was readily integrated into several different reactor configurations and was used heavily in chapters five and six for characterizing retentions of solutes in systems with packed beds.

In chapter three, simplification of dispersion in microfluidic devices to a system Fourier number was demonstrated. Furthermore, a novel simplification of the Damkohler number for flow reactors was demonstrated that relied on an estimate of the kinetic model and the Fourier number. These transformations enable both mixing and dispersion effects to be generalized in easily understandable charts, which should enable researchers across the field to rapidly evaluate whether mixing or dispersion effects are important based on preliminary flow data. The analysis was applied to a previously reported glycosylation reaction that was predicted to have both inadequate mixing and large deviations from plug flow. Improved mixing resulted in a three fold
increase in throughput, and estimates of the Damkohler number using the Fourier number were reasonable compared to the value calculated from experimental data. Furthermore, elimination of dispersion effects through the use of segmented flow resulted in the complete elimination of byproduct formation over the entire range of tube diameters investigated.

In chapter four, homogeneous catalyst recycling schemes involving thermomorphic solvents were evaluated. A major factor inhibiting the application of this technique was the limited number of synthetically useful thermomorphic solvents in the literature. To address this issue, a MATLAB program was written to screen solvent combinations for thermomorphic behaviors using UNIFAC. This work represents the first application of activity coefficient models to screen solvents for this type of behavior. Both previously unreported binary and ternary solvents were discovered and experimentally verified using continuous flow microreactors. Control of the critical solution temperature of the ternary solvents by varying composition was demonstrated for the first time. The ternary thermomorphic solvents discovered in this thesis represent a new class of thermomorphic solvent. Furthermore, the work in this chapter represented some of the first applications of microfluidic devices for extracting thermodynamic data from mixtures. Implementation of thermomorphic processes in flow systems was ultimately concluded to be quite challenging in practice due to the number of constraints of an operational system.

In chapter five, catalyst retention using fluorous physisorption was demonstrated to be a feasible technique for catalyst immobilization under continuous flow conditions. A silicon packed bed microreactor system was designed and fabricated for this project. Characterization of the retention of a fluorous tracer on fluorous silica gel revealed immobilization was feasible with selection of an appropriate solvent. Tracer retention in both very polar and very nonpolar
solvents was excellent, but for solvents of moderate polarity, such as methanol, retention was poor. Studies of a fluorous-tagged salen catalyst revealed excellent stability and activity under dilute feed conditions, which was the first successful demonstration of fluorous physisorption to immobilize a catalyst under flow conditions. As the salen catalyst was found to elute under higher conditions, a novel process for trapping and recycling catalysts immobilized under flow conditions was developed. This scheme used multiple beds in series with adjustment of the order of beds over time to effectively generate an infinite bed, though diffusive effects were demonstrated to have a deleterious effect on long term retention. A second study with a fluorous-tagged Hoveyda-Grubbs metathesis catalyst was carried out, though Hoveyda-Grubbs catalysts are known to be difficult to immobilize on a support. Significantly accelerated loss of activity compared to the salen catalyst was observed; further investigation revealed activity loss was due to deactivation and not elution, which is in agreement with the behavior of other covalently grafted metathesis catalysts. This example demonstrated that behavior of a physisorbed catalyst can be used to predict the behavior of a covalently grafted catalyst under flow conditions.

In chapter six, the first application of selective adsorption reactors for catalyst retention was demonstrated. The process relies on selective adsorption of one species onto a sorbent and is ideally suited to catalytic processes. A homogeneous catalyst and substrate are fed into a packed bed containing a sorbent, and the sorbent and catalyst are designed where the catalyst preferentially adsorbs on a support, which results in accumulation over time until complete saturation occurs. Under steady state conditions, the catalyst concentration in the packed bed is substantially higher than in the feed stream due to the sorption. The net result of this phenomenon is rate enhancement due to the higher catalyst concentration. This concept was
demonstrated using a perfluorinated scandium catalyst to effect a Diels-Alder reaction. Performing the reaction without adsorption of the catalyst resulted in <2% yield; conversely, a yield of 42% was achieved by incorporation of an adsorbent bed of fluorous silica gel. Further optimization resulted in achieving the equilibrium limited yield of 85%, which represented a turnover frequency enhancement of an order of magnitude compared to batch conditions. Application of the technique to the fluorous-tagged metathesis catalyst resulted in an increase in turnover frequency and turnover number; however, comparisons between the fluorous-tagged catalyst and the standard metathesis catalyst showed no improvement due in part to deactivation and in part due to the surprising affinity of the standard metathesis catalyst to fluorous silica gel. A mathematical model describing the system was developed, and a simple relationship to evaluate solid-liquid equilibrium coefficients from breakthrough curve measurements was derived.

7.2 Future Outlook

Continuous flow processing affords opportunities for running chemical reactions at elevated temperatures and pressures with the potential to have dramatically accelerated mass transfer and heat transfer. These advantages will allow enterprising researchers in the fine chemicals industry to develop new processes and chemistries that are either hazardous or unwieldy to run in batch.

Microreactors continue to gain ground as research tools with labs around the world; however, a relatively high cost barrier exists for new players. The cost of a single syringe pump can easily exceed the cost of chemicals consumed over an entire year by a diligent graduate student or post-doc. The development of low cost robust microreactors and syringe pumps would greatly accelerate the rate of adoption of continuous flow technology in academic research labs.
A significant barrier to entry for industrial players is the inability to produce relevant quantities using microreactors. The so-called “scale out” technique, where tens to thousands of microreactors are run in parallel, are conceptually simple but likely difficult to implement due to difficulties maintaining equal flow distribution. Robust techniques for scale-up from microreactors to production levels need further development, particularly for multi-phase applications.

Considerations for catalytic processes reveal several opportunities for future research. Droplet screening platforms are becoming more popular for library development\textsuperscript{89, 274}, and the incorporation of solid supported catalysts could broaden the capabilities of these platforms. The small volumes, excellent temperature control, and continuous flow operation make packed bed microreactors ideal tools for studying catalyst deactivation mechanisms of current and next generation catalysts, as real time monitoring of reactor effluent can be achieved. Recycle loops in biphasic and thermomorphic catalytic systems can lead to insight regarding the robustness of homogeneous catalysts, though this application is currently limited by the availability of small scale inline pumps.

The temporary immobilization techniques, such as fluorous physisorption, developed in this thesis offer unique advantages compared to covalent grafting of a support. The ability to quickly regenerate catalyst beds by desorption/adsorption processes may be attractive for deactivating catalysts. The development of selective adsorption reactors shows particular promise for reducing catalyst consumption, especially if tagged versions of a catalyst can be synthesized to promote adsorption of the catalyst to the sorbent. While this thesis demonstrated the applicability of selective adsorption reactors to equilibrium and byproduct forming reactions mathematically, these applications are currently unrealized in an experimental setting.
Ch 8. References


Appendix A: MATLAB programs for RTD analysis

This section contains the programs described in section 2.5 of this thesis. These files correctly work using MATLAB R2010B.

**RTDprog.m**

```matlab
function RTDprog(fname, n_inj, n_point, ax_vec)
% Reads a file and removes duplicate data. Writes the filtered data to another file called fname_filtered.txt. Calls function RTD_plotter for graphical interpretation of the data.
% Inputs:
%(fname: filename as a string ie 'RTDdata'
%n_inj: number of injections in file, integer
%in_opt: 1 input times manually
%2 input times as a table
%inj_table: Table containing n_inj rows and 3 columns, where
%column 1 is the injection time,
%column 2 is the end of the data
%column 3 is the flowrate in ul/min
%Author: Kevin D. Nagy, 2011
%Copyright 2011 Massachusetts Institute of Technology. All rights reserved

global data
if nargin == 0;
    fname = 'test'; n_inj = 2; n_point = 20; ax_vec = [0 3 0 5];
elseif nargin == 2;
    n_point = 20; ax_vec = [0 3 0 5];
end

inj_table = gen_A;
% Reads data from .txt files with 3 columns.
A = dlmread(strcat(fname, '.txt'), ':'); [nr nc] = size(A);
A = dlmread(strcat(fname, '.txt'), '%n', [0,1,nr-2,2]);

% Removes data where the measurement hasn't changed between time points
j = 1;
B = zeros(size(A));
for i = 2:length(A)
    if A(i,1) ~= A(i-1,1)
        j = j+1;
        B(j,:) = A(i,:);
    end
end

% Removes zeros from the end of the file
T = nonzeros(B(:,1));
B = [T B(1:length(T),2)];

% Writes filtered data to a separate file
dlmwrite(strcat(fname, '_filtered.txt'), B, '\');

% Plots the data for all injections
figure('Name', strcat(fname, ': all flows')); clf;
plot(B(:,1), B(:,2), 'kx');
xlabel('Time (s)'); ylabel('Absorbance\times100 (au)');
title(strcat('RTD measurement: ',fname, ' all injections'))

% Dummy data smoothing to check n_point
B_temp = zeros(length(B(:,1)),1);
for j = 1:length(B)-n_point,
    B_temp(j) = mean(B(j:j+n_point,2));
end
B3 = B_temp;
t3 = t(1:length(B3));
```

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for i = 1:n_inj
    %Reads injection times from gen_A file.
    st_exp = inj_table(i, 1);
    en_exp = inj_table(i, 2);
    flow = inj_table(i, 3);

    %Finds the indices for the start and end times for the injection
    st_pt = find(B(:, 1) >= st_exp, 1, 'first');
    e_pt = find(B(:, 1) <= en_exp, 1, 'last');

    %Normalizes time and concentration
    t = B(st_pt:e_pt, 1) - B(st_pt, 1); %Sets start time to 0
    data_new = B(st_pt:e_pt, 2); %All data
    slope = (mean(data_new(end-2*npoint:end)) - mean(data_new(1:2*npoint)))/t(end); %-Slope of data
    C = data_new - mean(data_new(1:2*npoint)); %-Intercept to 0
    C = C - slope.*t; %-Linear transformation

    %Actual data smoothing for the injection
    C_temp = zeros(length(C), 1);
    for j = 1:length(C)-npoint;
        C_temp(j) = mean(C(j:j+npoint));
    end
    C = C_temp;
    t = t(1:length(C));

    %Calculates parameters
    tot_C(i) = trapz(t, C);
    E = C./trapz(t, C);
    tau(i) = trapz(t, t.*E);
    t_theta = t./tau(i);
    E_theta = tau(i).*E;
    sig_t = (t-tau(i)).^2.*E;
    skew_t = (t-tau(i)).^3.*E;
    sig = sqrt(trapz(t_theta, (t_theta-1).^2.*E_theta));
    skew = (1/sig^1.5*trapz(t, (t-tau(i)).^3.*E))^(1/3);
    fprintf('
 Inj %d	 sig_t %3.5g', i, sig.^2)
    data{2*i-1} = t_theta;
    data{2*i} = E_theta;
end

fprintf('

Inj	 Area (C)	 Tau (s)')
for j = 1:n_inj
    fprintf('
%3.5g	%3.5g	%3.5g	%3.5g', j, tot_C(j), tau(j))
end
RTDplotter(fname, n_inj, 1)

return

**RTDplotter.m**

```matlab
function RTDplotter(fname, n_inj, n_exp)
% Function for comparing multiple series of injections against each other.
% Reads delimited text files that have been analyzed using the program
% "RTDprog".

% Inputs:
%   fname - file name without the extensions e.g. kn-254-3 for the file kn-254-3.txt
%   n_inj - number of injections for the data set
%   n_exp - number of experiments to plot together
% Author: Kevin D. Nagy, 2011
% Copyright 2011 Massachusetts Institute of Technology. All rights reserved

set(0,'DefaultAxesColorOrder', ...
    [0 0 1;
    0 0.5 1;
    0 0.75 0.75;
    0.75 0.75 0;
    0.25 0.25 0.25]);
Col = get(gca, 'ColorOrder');
L_plot = get(gca, 'LineStyle');
ax_vec = [0 2.5 0 6];

for j = 1:n_exp
    if j>1
        fname = input('Enter the next file to be read: ');
        n_inj = input('How many injections: ');
    end
    for i = 1:n_inj
        A = dlmread(strcat(fname, '_inj', num2str(i), '.txt'));
        t_data(2*i-1) = A(:,1); % Time data
        t_data(2*i) = A(:,2); % Concentration
        E_data(2*i-1) = A(:,3); % t_theta
        E_data(2*i) = A(:,5); % E_theta
    end
    if n_exp ~= 1
        figure(1); title('Comparison of injections - t vs C space')
        if j == 1
            clf
        end
    else
        figure('Name', strcat(fname, ': all injections - C space')); clf;
        title('All Injections')
    end
    if j == 1
        k = 1; l = 1;
    end
    for i = 1:n_inj
        if rem(k,length(Col)) == 0
            Col_plot = Col(k,:);
            k=k+1;
            L_plot = L_plot(l);
        else
            k=1; l=l+1;
            if l == 4
                l = 1;
            end
            Col_plot = Col(k,:);
        end
        plot(t_data(:,2*i-1), t_data(:,2*i), 'o', 'Color', Col_plot); hold on,
        L_plot, 'Color', Col_plot); hold on
```
% plot(t_data(:,2*i-1), t_data(:,2*i), 'Color', Col_plot); hold on; l_plot, 'Color', Col_plot); hold on
end
xlabel('t - s'); ylabel('Concentration'); title('All Injections')

if n_exp ~= 1
    figure(2); title('Comparison of injections - E space')
    if j == 1;
        clf
    end
else figure('Name', strcat(fname, ': all injections - E space')); clf;
    title('All Injections')
end
if j == 1
    m = 1; n = 1;
end
for i = 1:n_inj
    if rem(k,length(Col)) ~= 0
        Col_plot = Col(m,:);
        m=m+1;
    l_plot = L_plot(n);
else
    m=1; n=n+1;
    if n == 4
        n = 1;
    end
    Col_plot = Col(m,:);
end
plot(E_data(:,2*i-1), E_data(:,2*i), 'o', 'Color', Col_plot); hold on
plot(E_data(:,2*i-1), E_data(:,2*i), 'Color', Col_plot); hold on
end
xlabel('\Theta'); ylabel('E(\Theta)');
axis(ax_vec);
end
 return

 gen_A.m
 function A = gen_A
 %Input times and flowrates for use with RTD_prog.
 %Data should be input as rows with three columns
 %Column 1: Start of injection, [s]
 %Column 2: End of injection, [s]
 %Column 3: Volumetric flowrate, microliter/min
 %Example experiment of three injections at 20 minutes, 28 minutes, and 35 min 30 s
 %with experimental duration of ~7 min and flowrates of
 %25 microliter per minute:
 % Test
 % A = [1200 1620 25
 % 1680 2100 25
 % 2130 2500 25];
 % Author: Kevin D. Nagy, 2011
 % Copyright 2011 Massachusetts Institute of Technology. All rights reserved

 RTD_cross.m
 function RTD_cross(fname, n_inj, n_point, ax_vec, noise, B_vec)
 %Reads a fname.txt file and removes duplicate data. Writes the filtered data
 %to another file called fname_filtered.txt. Calls function RTD_analysis
 %for graphical interpretation of the data
 %Inputs:
 % fname: filename as a string ie 'RTDdata'
 % n_inj: number of injections in file, integer
 % n_point: number of points to calculate moving average

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if nargin == 0;
    fname = 'test'; n_inj = 2; n_point = 20; ax_vec = [0 3 0 5];
    noise = 0.02; B_vec = [10 15];
elseif nargin == 2;
    n_point = 20; ax_vec = [0 3 0 5];
    n_point = 20; B_vec = [10 15]
else if nargin == 4;
    n_point = 20; B_vec = [10 15]
end
offset = -6;
inj_table = gen_A;
A = dlmread(strcat(fname,'.txt'), ':'); [nr nc] = size(A);
A = dlmread(strcat(fname, '.txt'), '%n', [0,1,nr-2,2]);

%Removes data where the measurement hasn't changed between time points
j = 1;
B = zeros(size(A)); %B(1,:) = A(1,:);
for i = 2:length(A)
    if A(i,1) ~= A(i-1,1)
        j = j+1;
        B(j,:) = A(i,:);
    end
end

%Removes zeros from the end of the file
t = nonzeros(B(:,1));
B = [t B(1:length(t),2)];

%Calls write function to separate file
dlmwrite(strcat(fname,'_filtered.txt'), B, '\t');

%Plots data for all injections
figure('Name', strcat(fname, ': all flows')); clf;
plot(B(:,1), B(:,2), 'k');
xlabel('Time (s)'); ylabel('Absorbance x 100 (au)');
title(strcat('RTD measurement: ', fname, ' all injections'))

%Dummy Data smoothing
B_temp = zeros(length(B)-n_point,1);
for k = 1:length(B)-n_point
    B_temp(k) = mean(B(k:k+n_point,2));
end
t = t(1:length(B_temp));
dt = t(4)-t(3);
B = [t B_temp];
figure('Name', 'Smoothed data via moving average'); plot(t, B_temp, 'x'); title('Smoothed data via moving average')

%Low pass filter
B_diff = B_temp(2:end) - B_temp(1:end-1); %Forward difference
figure('Name', 'Differential data point scanning'); plot(t(2:end), abs(B_diff)); title('Differential data point scanning')
[i, j] = find(abs(B_diff)<noise);
B_out = B(i,2);
t_out = B(i,1);
figure('Name', 'Smoothed data with peak points removed'); plot(t_out,B_out, 'x');
title('Smoothed data with peak points removed')
%Find points that are outside range
[i2, j2] = find(B_out<B_vec(1) | B_out > B_vec(2));
B_out2 = zeros(size(B_out));
B_out2(i2) = B_out(i2)+offset;
% t_out = t_out(i2);
% length(t_out), length(B_out2)
figure('Name', 'Transition points + second phase data removed'); plot(t_out,B_out2, 'x')
title('Transition points + second phase data removed')
B = [t_out B_out2];

for i = 1:n_inj
    %Reads injection times from gen_A file.
st_exp = inj_table(i,1);
en_exp = inj_table(i,2);
flow = inj_table(i,3);

    %Finds the indices for the start and end times for the injection
st_pt = find(B(:,1) >= st_exp, 1, 'first');
e_pt = find(B(:,1) <= en_exp, 1, 'last');

    %Normalizes time and concentration
t = B(st_pt:e_pt,1) - B(st Pt,1); %Sets start time to 0
[i3, j3] = find(B(stpt:ept,2)== offset);

    %Linear transformation of data
slope = (mean(C(end-2*n_point:end)) - mean(C(1:2*n_point)))/t(end);
C = C - slope.*t;
C(i3) = 0; %Sets second phase data equal to 0

    %Calculates parameters
totC(i) = trapz(t,C);
E = C./trapz(t,C);

    tau(i) = trapz(t, t.*E);
t_theta = t./tau(i);
E_theta = tau(i).*E;
sig2 = (t-tau(i)).^2.*E;
skew_t = (t-tau(i)).^3.*E;
sig = sqrt(trapz(t_theta, (t_theta-1).^2.*E_theta));
skew = (1/sig^1.5*trapz(t,(t-tau(i)).^3.*E_theta))^(1/3);

    data{2*i-1) = t_theta;
data{2*i} = E_theta;

    %Writes the data for each injection to a text file
filt_data = [t C t_theta E E_theta sig_t skew_t];
dlmwrite(strcat(fname, '_inj_', num2str(i), '.txt'), filt_data, '
end

for j=1:n_inj
    fprintf('Inj	Area (C)	Tau (s)
%3.5g	%3.5g	%3.5g	%3.5g', j, totC(j), tau(j))
end

RTDplotter(fname, n_inj, 1)
Appendix B: Analytical $\chi$ parameter derivations

In this appendix we derive the functional form of $\chi$ to enable estimation of the Dahmkohler number of the generic form given by equation S2-1 for various kinetic models.

$$Da = \frac{\chi}{Fo}. \quad \text{(S2-1)}$$

**First order reaction system**

Rate model:

$$\frac{dA}{dt} = -kA \quad \text{(S2-2)}$$

Dahmkohler number:

$$Da_1 = \frac{kd_A^2}{4D} \quad \text{(S2-3)}$$

Expression for conversion:

$$k\tau = -\ln(1-X_A) \quad \text{(S2-4)}$$

thus

$$k = -\frac{\ln(1-X_A)}{\tau} \quad \text{(S2-5)}$$

Dahmkohler number in terms of conversion and residence time:

$$Da_1 = -\ln(1-X_A) \frac{d_A^2}{4\tau D} = -\frac{\ln(1-X_A)}{Fo} \quad \text{(S2-6)}$$

Thus, $\chi_1 = -\ln(1-X_A)$ \quad \text{(S2-7)}$

**Second order reaction system**

Rate model:

$$\frac{dA}{dt} = -kA^2 \quad \text{(S2-8)}$$

Dahmkohler number:

$$Da_2 = \frac{kA_0 d_A^2}{4D} \quad \text{(S2-9)}$$

Expression for conversion:

$$X_A = \frac{kA_0 t}{1 + kA_0 t} \quad \text{(S2-10)}$$
thus

\[ k_A_0 = \frac{X_A}{1 - X_A} \]  

(S2-11)

And the Dahmkohler number in terms of conversion and residence time:

\[ Da_2 = \frac{X_A}{1 - X_A} \frac{d_i^2}{4\tau D} = \frac{X_A}{1 - X_A} \frac{1}{Fo} \]  

(S2-12)

Thus, \( \chi_2 = \frac{X_A}{1 - X_A} \)  

(S2-13)

1\textsuperscript{st} order in A and B, stoichiometric feeds

Making the substitution \( A = B \) results in the same functional form of \( \chi \) as above.

Rate model:

\[ \frac{dA}{dt} = -kAB \]  

(S2-14)

Dahmkohler number:

\[ Da_A = Da_B = \frac{kA_0 d_i^2}{4D} \]  

(S2-15)

Expression for conversion:

\[ X_A = \frac{kA_0 t}{1 + kA_0 t} \]  

(S2-16)

thus

\[ kA_0 = \frac{X_A}{1 - X_A} \]  

(S2-17)

And the Dahmkohler number in terms of conversion and residence time:

\[ Da_1 = \frac{X_A}{1 - X_A} \frac{d_i^2}{4\tau D} = \frac{X_A}{1 - X_A} \frac{1}{Fo} \]  

(S2-18)

Thus, \( \chi_2 = \frac{X_A}{1 - X_A} \)  

(S2-19)

1\textsuperscript{st} order in A and B, non-stoichiometric feeds

The key transformation is to write \( A \) and \( B \) in terms of their stoichiometric feed ratio \( M \).

Stoichiometric feed ratio:

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\[ M = \frac{B_0}{A_0} \]  

Rate model:
\[ \frac{dA}{dt} = -kAB \quad \text{and} \quad \frac{dB}{dt} = -kAB \]  

Dahmkohler number:
\[ Da_B = \frac{kA_0 d_i^2}{4D} \]  
\[ Da_A = \frac{kB_0 d_i^2}{4D} = MDa_B \]  

Rate model in terms of conversion:
\[ A = A_0 \left(1 - X_A\right) \]  
\[ B = B_0 - A_0 X_A = A_0 \left(M - X_A\right) \]  
\[ \frac{dX_A}{dt} = kA_0 \left(1 - X_A\right) \left(M - X_A\right) \]  

Solution to equation S2-X:
\[ \frac{1}{M-1} \ln \left( \frac{M-X_A}{M-MX_A} \right) = kA_0 t \]  

thus the Dahmkohler numbers in terms of conversion and residence time:
\[ Da_B = \frac{1}{M-1} \ln \left( \frac{M-X_A}{M-MX_A} \right) \frac{d_i^2}{4\tau D} = \frac{1}{M-1} \ln \left( \frac{M-X_A}{M-MX_A} \right) \frac{1}{Fo} \]  
\[ Da_A = MDa_B = \frac{M}{M-1} \ln \left( \frac{M-X_A}{M-MX_A} \right) \frac{1}{Fo} \]

Thus, \( \chi_B = \frac{1}{M-1} \ln \left( \frac{M-X_A}{M-MX_A} \right) \) and \( \chi_A = \frac{M}{M-1} \ln \left( \frac{M-X_A}{M-MX_A} \right) \)

1\(^{st}\) order in A and B, nonstoichiometric feeds, autocatalytic in B

Again writing \( A \) and \( B \) in terms of their stoichiometric feed ratio \( M \).

Stoichiometric feed ratio:
\[ M = \frac{B_0}{A_0} \]  

Rate model:
\[
\frac{dA}{dt} = -kAB \quad \text{and} \quad \frac{dB}{dt} = kAB
\]

Dahmkohler number:

\[
Da_B = \frac{kA_0d_A^2}{4D}
\]
\[
Da_A = \frac{kB_0d_B^2}{4D} = MDa_B
\]

Rate model in terms of conversion:

\[
A = A_0(1 - X_A)
\]
\[
B = B_0 + A_0X_A = A_0(M + X_A)
\]
\[
\frac{dX_A}{dt} = kA_0(1 - X_A)(M + X_A)
\]

Solution to equation S2-X:

\[
\frac{1}{M+1} \ln \left( \frac{M + X_A}{X_A - 1} \right) = kA_0t
\]

thus the Dahmkohler numbers in terms of conversion and residence time:

\[
Da_B = \frac{1}{M+1} \ln \left( \frac{M + X_A}{X_A - 1} \right) = \frac{1}{M+1} \ln \left( \frac{M + X_A}{X_A - 1} \right) \frac{1}{Fo}
\]
\[
Da_A = MDa_B = \frac{M}{M+1} \ln \left( \frac{M + X_A}{X_A - 1} \right) \frac{1}{Fo}
\]

Thus, \( \chi_B = \frac{1}{M+1} \ln \left( \frac{M + X_A}{X_A - 1} \right) \) and \( \chi_A = \frac{M}{M+1} \ln \left( \frac{M + X_A}{X_A - 1} \right) \)

1st order in A, negative 1st order in B

Again writing \( A \) and \( B \) in terms of their stoichiometric feed ratio \( M \).

Stoichiometric feed ratio:

\[
M = \frac{B_0}{A_0}
\]

Rate model:

\[
\frac{dA}{dt} = \frac{dB}{dt} = -k \frac{A}{B}
\]

Dahmkohler number:
\[ Da_B = \frac{kA_0 d_t^2}{B_0^2 4D} \quad (S2-44) \]
\[ Da_A = \frac{kd_t^2}{4B_0 D} = MDa_B \quad (S2-45) \]

Rate model in terms of conversion:
\[ A = A_0 (1 - X_A) \quad (S2-46) \]
\[ B = B_0 - A_0 X_A = A_0 (M - X_A) \quad (S2-47) \]
\[ \frac{dX_A}{dt} = \frac{k}{A_0} \frac{1 - X_A}{M - X_A} \quad (S2-48) \]

Solution to equation S2-X:
\[ X_A - (M - 1) \ln(1 - X_A) = \frac{kt}{A_0} = \frac{Mkt}{B_0} \quad (S2-49) \]

thus the Dahllmohler numbers in terms of conversion and residence time:
\[ Da_A = \frac{1}{M} \left[ X_A - (M - 1) \ln(1 - X_A) \right] \frac{1}{Fo} \quad (S2-50) \]
\[ Da_B = \frac{Da_A}{M} = \frac{1}{M^2} \left[ X_A - (M - 1) \ln(1 - X_A) \right] \frac{1}{Fo} \quad (S2-51) \]

Thus, \( X_A = \frac{1}{M} \left[ X_A - (M - 1) \ln(1 - X_A) \right] \) and \( X_B = \frac{1}{M^2} \left[ X_A - (M - 1) \ln(1 - X_A) \right] \) \quad (S2-52)

2\textsuperscript{nd} order in A, 1\textsuperscript{st} order in B

Again writing \( A \) and \( B \) in terms of their stoichiometric feed ratio \( M \).

Stoichiometric feed ratio:
\[ M = \frac{B_0}{A_0} \quad (S2-53) \]

Rate model:
\[ \frac{dA}{dt} = -kA^2 B \quad \text{and} \quad \frac{dB}{dt} = -kB^2 A \quad (S2-54) \]

Dahllmohler number:
\[ Da_B = \frac{kA_0^2 d_t^2}{4D} \quad (S2-55) \]
\[ Da_A = \frac{kA_0 B_0 d_t^2}{4D} \quad (S2-56) \]

Rate model in terms of conversion:
\[ A = A_0 (1 - X_A) \]  
(S2-57)

\[ B = B_0 - A_0 X_A = A_0 (M - X_A) \]  
(S2-58)

\[ \frac{dX_A}{dt} = kA_0^2 (1 - X_A)^2 (M - X_A) \]  
(S2-59)

Solution to equation S2-X:

\[ \frac{1}{(M-1)^2} \left[ \ln \left( \frac{M - MX_A}{M - X_A} \right) + \frac{MX_A - X_A}{1 - X_A} \right] = kA_0^2 t \]  
(S2-60)

thus the Dahmkoehler numbers in terms of conversion and residence time:

\[ Da_B = \frac{1}{(M-1)^2} \left[ \ln \left( \frac{M - MX_A}{M - X_A} \right) + \frac{MX_A - X_A}{1 - X_A} \right] \frac{1}{Fo} \]  
(S2-61)

\[ Da_A = MDa_B = \frac{M}{(M-1)^2} \left[ \ln \left( \frac{M - MX_A}{M - X_A} \right) + \frac{MX_A - X_A}{1 - X_A} \right] \frac{1}{Fo} \]  
(S2-62)

Thus,

\[ \chi_B = \frac{1}{(M-1)^2} \left[ \ln \left( \frac{M - MX_A}{M - X_A} \right) + \frac{MX_A - X_A}{1 - X_A} \right] \]

and

\[ \chi_A = \frac{M}{(M-1)^2} \left[ \ln \left( \frac{M - MX_A}{M - X_A} \right) + \frac{MX_A - X_A}{1 - X_A} \right] \]  
(S2-63)
Appendix C: MATLAB program for binary UNIQUAC calculations

This section contains the programs described in section 2.5 of this thesis. These files correctly work using MATLAB R2010B. Additional data sources are required for program functionality.

**TSS_UNIQUAC.m**

```matlab
function TSS_UNIQUAC(compounds, Tmin, Tmax)
%This program predicts phase splitting based on Gibbs energy of mixing and
%the UNIQUAC model based for a very limited number of chemical species.
%Specifically, species listed and interaction parameters from
%Tester and Modell, Thermodynamics and Its Applications, 3 ed.,
%1997, p.491-492. are included in the Excel spreadsheet
%"UNIQUAC parameters.xls" to
%Function which is available upon request.
%Alternate input sources of physical parameters and interaction data should
%be possible.

%Inputs: compounds: vector with indices of species A and B from "UNIQUAC
%parameters.xls"
%Tmin: lower temperature for calculation
%Tmax: upper temperature for calculation
%Author: Kevin D. Nagy
%Copyright 2011 Massachusetts Institute of Technology. All rights reserved

if nargin == 0
    %Test case of DMF:heptane
    compounds = [12 8]; Tmin = 273; Tmax = 423;
end

[r q qp a comps] = UNIQUAC_S_LIST(compounds)
x = 0.01:0.01:0.99; x2 = 1-x; x1=x;
T = Tmin:(Tmax-Tmin)/20:Tmax;
tau2l = exp(-a(1,2)/T); tau2l = exp(-a(2,1)/T);

thpl = x1*qp(1)/(x1*(qp(1)-qp(2))+qp(2));

thp2 = 1-thpl;

d1_thpl = qp(1)*qp(2)/(x1*(qp(1)-qp(2))+qp(2)).^2;
d2_thpl = qp(2)*(1-x1).*(d1_thpl+dl_thpl*tau2l(i)).^2/den_b.^2;

dG2_ID = 1./(x.*(1-x));
dG2_comb = (r(1)-r(2)).^2./((x1*(r(1)-r(2))+(r(2))).^2-(z/2)*(r(1)*q(2)-r(2)*q(1)).^2/((x1*(q(1)-q(2))+(q(2))).^2);　T1 =-1000*ones(size(dG_tot));

for i=1:length(T)
    den_a = thpl+thp2*tau2l(i);
    den_b = thp2+thpl*tau2l(i);
    dG_res_a = -(2*qp(1).*d1_thpl+dl_thpl*thp2+thpl*tau2l(i))./den_a;
    dG_res_b = (2*qp(2).*d2_thpl+thpl*tau2l(i))./den_b + qp(2).*(1-x1).*(1-x1).
    dG_res_c = qp(1).*x1.*d1_thpl+thp2*thpl*tau2l(i)).^2/den_a.^2;
    dG_res_d = qp(2).*(1-x1).*d1_thpl+thp2*thpl*tau2l(i)).^2/den_b.^2;
end
```

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num_a = 2*qp(1)^2*qp(2)^2*(tau21(i)-1)./(x1*(qp(1)-qp(2))+qp(2)).^3;
num_b = 2*qp(2)^2*qp(1)^2*(-tau12(i)*qp(2)*x1*qp(1)+qp(2)*x1-qp(1))
   +qp(1)*tau12(i)*qp(1)*tau12(i)*x1*tau12(i)./(x1*(qp(1)-qp(2))
   +qp(2)).^3;
num_c = -qp(2)^3*(x1-1)*qp(1)^2*(tau12(i)-1)^2./x1*(qp(1)-qp(2))
   +qp(2)).^4;
num_d = qp(1)*x1*qp(1)^2*qp(2).^2*(tau21(i)-1)^2./(x1*(qp(1)-qp(2))
   +qp(2)).^4;
dG2_res(i,:) = dG_res_a+dG_res_b+dG_res_c+dG_res_d;
dG_tot(i,:length(x)) = dG2_ID + dG2_comb + dG2_res(i,:);
[ii, jl] = find(dG_tot(i,:)<=0);
end

figure(1); clf
plot(x,T1, 'x'); axis([0 1 T(1)-283 T(end)-263]);
extlabel('x_1 (mol)'); ylabel('Temperature (C)');
formatp(gca);
v = axis;
for k = 1:j
    Y(k) = 0.05*K*v(3) + (1-0.05*k)*v(4);
    text(0.6, Y(k), t_comp{k});
end
ptitle = sprintf('%s %s %d %d dG', comps{1}, comps{2}, Tmin, Tmax); saveas(gcf, ptitle, 'bmp')

function [r q qp aij comps] = UNIQUAC_S_LIST(vec)
% Extracts solvent data for use in the UNIQUAC file
% Inputs:
% vec: solvent coordinates
% Outputs:
% r: vector of component relative volume fraction
% q: vector of relative area fraction
% a: matrix of interaction areas, inverse K
% For a list of working compounds, see COMP_LIST.
% Currently only works with binaries
% Author: Kevin Nagy, 04/24/2008
[r_q_data, comp_list] = xlsread('UNIQUAC parameters.xls', ...
   'structural', 'a2:d200');
aij_data = xlsread('UNIQUAC parameters.xls', 'en_matrix', 'c2:x23');
r = r_q_data(vec,1); q = r_q_data(vec,2); qp = r_q_data(vec,3);
aij = aij_data(vec, vec);
comps = comp_list(vec, 4);
return

function formatp(y)
% Formats plots
set(y, 'FontSize', 14); set(y, 'FontName', 'Arial', 'FontWeight', 'bold');
set(get(y), 'XMinorTick', 'on', 'YMinorTick', 'on', 'Box', 'on')
set(get(y), 'XLabel', 'FontName', 'Arial', 'FontSize', 14)
set(get(y), 'YLabel', 'FontName', 'Arial', 'FontSize', 14)
set(get(y), 'Title', 'FontName', 'Arial', 'FontSize', 12)
set(gca, 'FontName', 'Arial', 'FontSize', 14, 'FontWeight', 'bold');
return
Appendix D: MATLAB programs for binary UNIFAC-Do calculations

This program contains software to calculate phase splitting using the modified UNIFAC (Dortmund) model as described in section 4.6 of this thesis. These files correctly work using MATLAB R2010B. The shell program “unifac_screen” can be used for combinatorial screening. Additional data sources are required for program functionality.

**TSS_UNIFAC.m**

```
function hit = TSS_UNIFAC(compounds, Tmin, Tmax, plot_on, screen)
%Calculates the activity coefficients of binary systems using the modified
%UNIFAC (Dortmund) system.
%Inputs: compounds - vector of components, only works for binary
%       Tmin - minimum temperature
%       Tmax - maximum temperature
%       plot_on - 1 to plot results, 0 to not plot
%       screen - determines whether excel data is loaded, 0 to open files
%Outputs: hit - result indicates whether thermomorphic behavior was detected
%         -1: monophasic over the entire temp range
%         0: thermomorphic
%         1: biphasic over the entire temp range
%         2: missing interaction parameter
%
% This program requires the following .xls data sources to perform calculations. Available upon request.
%solventsMod2 - list of solvents and associated functional groups of each solvent
%Modparameters.xls - matrix of temperature dependent interaction parameters
%ModRQMatrix - structural data for each functional group
%Author: Kevin D. Nagy, Aug 16, 2009
%Copyright 2011 Massachusetts Institute of Technology. All rights reserved
% clc, close all

global phi_data RQ_mat group_mat group_ID xl names comps compounds Param RQ_data

if nargin == 0
    compounds = [22 17]; Tmin = 273; Tmax = 398; plot_on=1; screen = 0;
end

xl = 0:0.01:1; x2 = 1-xl;
T = Tmin:(Tmax-Tmin)/20:Tmax;

if screen == 0
    clear names comps
    [null, names] = xlsread('solventsMod2', 'complist', 'al:a50');
    comps={[names{compounds]}];
    length(names)
    %Temp dependent activation parameters of type exp(-(A+BT+CT^2)/T)
    phi_data = xlsread('Modparameters.xls', 'parammatrix', 'a1:a249');

    %molecular r_i's, q_i's, and group contributions
    RQ_data = xlsread('ModRQMatrix.xls');
    Param = xlsread('solventsMod2.xls', 'matrix');
end

hit_a = 0; hit_b = 0;
```
comps_disp = {names{compounds}};

nu_mat = Param(compounds,:); %Matrix of all chem groups with frequency
nu_vect = sum(nu_mat(1:end,:)); %Total number of chemical groups
group_ID = find(nu_vect>0); %Index of chemical group

group_mat = nu_mat(:,group_ID); %Num of each chem group in each mol

RQ_mat = RQ_data(group_ID,3); %Group pairing of each molecule, calculating phi

nu_vect = sum(numat(1:end,:)); 'Total number of chemical groups

groupID = find(nuvect=0); %Index of chemical group

group_mat = nu_mat(:,groupID); %Num of each chem group in each mol

group ind = RQ data(group_ID,3)'; %Group pairing of each molecule, calculating phi

RQmat = RQdata(group_ID,1:2)'; %Molecular properties of each molecule, R=row 1, Q=row 2

%Calculate non-temperature dependent properties
g_ID = x1.*log(x1)+(1-x1).*log(1-x1);
g_comb = calc_g_comb;
[chi pure, theta pure, chi mix, theta mix] = calc_chi;

%Preallocation of variables for speed
g_tot = zeros(length(T),length(x1));
g_ex = g_tot;
g_tot_ex = zeros(length(compounds), length(x1));

end

for t=1:length(T)

%Interaction parameters
[phi phi_test] = calc_int(group ind,T(t));
if phi_test == 2 %Missing parameter
hit = 2;
return
end

%Pure components, just wait for the 3D indexing
for i = 1:length(compounds)
for k = 1:length(group_ID)
 if group mat(i,k)==0
 g_res pure_a(i,k) = 1-log(sum(theta pure(i,:).*phi(:,k)));
 for m = 1:length(group_ID)
g_res pure_b(m,k) = -theta pure(i,m)*phi(k,m)/sum(theta pure(i,:).*phi(:,m));
 end
 g_res pure tot(i,k) = sum(RQmat(2,k)*(g res pure a(i,k)+sum(gres pure_b(:,k))));
 else g_res pure tot(i,k)=0; g_res pure a(i,k)=0; g_res pure_b(:,k) = 0;
 end
 end

%Mixtures, just wait for the 3D indexing
for z= 1:length(x1)
 for k = 1:length(group_ID)
 g_res mix b = zeros(length(group_ID),length(group_ID), length(group_ID));
 for m = 1:length(group_ID)
g_res mix_a(k,z) = 1-log(sum(theta mix(:,z).*phi(:,k)));
 for m = 1:length(group_ID)
g_res mix_b(m,k,z) = -theta mix(m,z)*phi(k,m)/sum(theta mix(:,z).*phi(:,m));
 end
 g_res mix tot(k,z) = RQ_mat(2,k)*(g_res mix a(k,z)+sum(g_res mix b(:,k,z)));
 end
 for k = 1:length(group_ID)
 g_res mix tot(k,z) = RQ_mat(2,k)*(g_res mix a(k,z)+sum(g_res mix b(:,k,z)));
 end
 end

%Calculate residual portion for each compound
for i = 1:length(compounds)
    for z = 1:length(xl)
        g_restot(i, z) = sum(groupmat(i, :) .* (gresmixtot(:, z) - grespuretot(i, :)));
    end
end
% Calculate total excess for each compound
for i = 1:length(compounds)
    g_totex(i, 1:length(xl)) = (g_restot(i, 1:length(xl)) + g_comb(i, 1:length(xl)));  
end
% Calculate total Gibbs Free Energy
for i = 1:length(xl)
    g_ex(t, 1:length(xl)) = xl.*g_totex(1, 1:length(xl)) + (l-xl).*g_tot(t, 1:length(xl));
    g_tot(t, 1:length(xl)) = g_ex(t, 1:length(xl)) + g_ID;
end
dGdxl = zeros(length(t), length(xl)-2);
dG2dxl2 = dGdxl;
% Calculate second derivative and find regions less than zero
for i = 1:length(T)
    for j = 2:length(xl)-1
        dGdxl(i, j) = (g_tot(i, j+1)-g_tot(i, j-1))/(2*dxl);
        dG2dxl2(i, j) = (g_tot(i, j+1)+g_tot(i, j-1)-2*g_tot(i, j))/(dxl^2);
    end
end
for i = 1:length(T)
    for j = 1:length(compounds)
        t_comp{j} = sprintf('Component %d: %s', j, compsdisp{j});
    end
end
figure(1); hold on
plot(xl, g_tot)
xlabel('x_1 (mol)'); ylabel('\Delta G_{\text{mix}}/RT'); formatp(gca)
v = axis;
text(0.1, 0.05*v(3) + 0.95*v(4), t1)
for k = 1:length(T)
    Y(k) = 0.05*k*v(3) + (1-0.05*k)*v(4);
    text(0.6, Y(k), tcomp{k})
end
ptitle = sprintf('%s %s %d %d \Delta G', compsdisp{1}, compsdisp{2}, Tmin, Tmax);
saveas(gcf, ptitle, 'bmp')
figure(2); plot(xl, T2, 'x')
axis([0 1 T(l)-283 +T(end)-263])
xlabel('x_1 (mol)'); ylabel('Temperature')
title('T-x diagram using UNIFAC'); formatp(gca)
v = axis;
text(0.1, 0.05*v(3)+ 0.95*v(4), t1)
for k = 1:j
    Y(k) = 0.05*k*v(3) + (1-0.05*k)*v(4);
text(0.6, Y(k), tcomp{k})
end
ptitle = sprintf('%s %s %d %d T-x', comps_disp{1}, comps_disp{2}, Tmin, Tmax);
saveas(gcf, ptitle, 'bmp')
figure(3); plot(xl(2:end), dGdxl); title('1st derivative')
figure(4); plot(xl(2:end), dG2dxl2); title('2nd derivative')
% figure(5); plot(xl,
% pause
end
return
%%%%%%%%%%%%%%%%End main function %%%%%%%%%%%%%%%%%%Begin interaction parameter calculation%%%%%%%%%%%%%%%%%%%%%%%%%%%% function [phi, phitest] = calc_int(group_ind, Temp)
global phi_data
phitest = 1;
phi = ones(length(group_ind), length(group_ind));
for i = 1:length(group_ind)
    for j = 1:length(group_ind)
        if group_ind(i) ~= group_ind(j)
            A = phi_data(group_ind(i), group_ind(j));
            B = phi_data(group_ind(i) + 83, group_ind(j));
            C = phi_data(group_ind(i) + (83*2), group_ind(j));
            if A == -1 & B == -1 & C == -1
                fprintf('
Unknown interaction parameter for %g, %g', i, j)
                phitest = 2;
            else
                phi(i, j) = exp(-(A + B * Temp + C * Temp.^2) ./ Temp);
            end
        end
    end
end
return
%%%%%%%%%%%%%%%%End interaction parameter calculation%%%%%%%%%%%%%%%%%%%%%%%%%%%%Begin chi and theta calculation%%%%%%%%%%%%%%%%%%%%%%%%%%%% function [chi_pure, theta_pure, chi_mix, theta_mix] = calc_chi
global RQ_mat group_mat compounds group_ID xl
chi_pure = zeros(length(compounds), length(group_ID));
theta_pure = zeros(length(compounds), length(group_ID));
chi_mix = zeros(length(xl), length(group_ID));
theta_mix = zeros(length(group_ID), length(xl));
for i = 1:length(compounds)
    for j = 1:length(group_ID)
        chi_pure(i, j) = group_mat(i, j) / sum(group_mat(i, :));
    end
    for k = 1:length(group_ID)
        theta_pure(i, k) = chi_pure(i, k) * RQ_mat(2, k) / sum(chi_pure(i, :) .* RQ_mat(2, :));
    end
end
for j = 1:length(group_ID)
    chi_mix(1:length(xl), j) = (xl .* (group_mat(1, j) - group_mat(2, j)) + group_mat(2, j)) ./ (xl .* sum(group_mat(1, :)) - sum(group_mat(2, :)) + sum(group_mat(2, :)))
end
for z = 1:length(xl)
    for j = 1:length(group_ID)
        theta_mix(j, z) = RQ_mat(2, j) .* chi_mix(z, j) ./ sum(RQ_mat(2, :) .* chi_mix(z, :));
end
% pause
end
function g_comb = calc_g_comb

for i = 1:length(compounds)
    r(i) = sum(group_mat(i,:).*RQmat(1,:)); % Specific radius
    q(i) = sum(group_mat(i,:).*RQmat(2,:)); % Specific surface area
end

V = zeros(length(compounds), length(xl));
F = V; Vp = V; g_comb = V;

for i = 1:length(compounds)
    V(i, 1:length(xl)) = r(i)./(xl*(2*r(l)-sum(r))+sum(r)-r(l));
    F(i, 1:length(xl)) = q(i)./(xl*(2*q(l)-sum(q))+sum(q)-q(l));
    Vp(i, 1:length(xl)) = r(i)^(3/4)./(xl*(2*r(l)^(3/4)-sum(r.^(3/4)))+sum(r.^(3/4))-r(l)^(3/4));
    g_comb(i,1:length(xl)) = 1-Vp(i,:)+log(Vp(i,:))...-5*q(i)*(1-V(i,:)./F(i,:))+log(V(i,:)./F(i,:));
end

return

function formatp(y)

set(y,'FontName', 'Arial','FontSize', 12,...
'XMinorTick', 'on', 'YMinorTick', 'on', 'Box', 'on')
set(get(y, 'XLabel'), 'FontName', 'Arial','FontSize', 12)
set(get(y, 'YLabel'), 'FontName', 'Arial','FontSize', 12)
set(get(y, 'Title'), 'FontName', 'Arial',...'
'FontSize', 12, 'FontWeight', 'bold')
set(gca,'FontName', 'Arial','FontSize', 12,...
'XMinorTick', 'on', 'YMinorTick', 'on', 'Box', 'on')

return

function unifac_screen

Shell program for performing combinatorial screens for thermomorphic characteristics.
Requires TSS_UNIFAC.m to function and external data sources described in TSS_UNIFAC.m to function.
Author: Kevin D. Nagy
Copyright 2011 Massachusetts Institute of Technology. All rights reserved

clc, close all

global phi_data names comps Param RQ_data

[null, names] = xlsread('solventsMod2', 'complist', 'a1:a50');
comps={names{l:length(names)});

% Temp dependent activation parameters % if type exp(-(A+B*T+C*T^2)/T)
phi_data = xlsread('Modparameters.xls', 'parammatrix', 'a1:ce249');

% Molecular r_i's, q_i's, and group contributions
RQ_data = xlsread('ModRQMatrix.xls');
Param = xlsread('solventsMod2.xls', 'matrix');
hit = zeros(length(names), length(names));
tic
for i = 1:length(names)
    for j = i+1:length(names)
        fprintf('
'i='g,'j='g', i, j)
        hit(i,j) = TSS_UNIFAC([i j], 273, 423, 0, 1);
    end
end

m = 1; n = 1; p = 1;
for i=1:length(names)
    for j = i+1:length(names)
        % Thermomorphic cases
        if hit(i,j) == 0
            thermo(m,1:2) = [i j];
            m = m+1;
        elseif hit(i,j) == 1
            biphasic(p,1:2) = [i j];
            p = p+1;
        elseif hit(i,j) == 2
            no_param(n,1:2) = [i j];
            n = n+1;
        end
    end
end

hit
for i = 1:m-1
    null = TSS_UNIFAC([thermo(i,1) thermo(i,2)], 273, 423, 1, 1);
end

fprintf('
Possible thermomorphic cases')
fprintf('
Comp 1	Comp 2	i	j')
for i = 1:m-1
    fprintf('
%s 	%s 	%g 	%g', comps{thermo(i,1)}, comps{thermo(i,2)}, thermo(i,1), thermo(i,2))
end

fprintf('
Missing parameter cases')
fprintf('
Comp 1	Comp 2	i	j')
for i = 1:n-1
    fprintf('
%s 	%s 	%g 	%g', comps{no_param(i,1)}, comps{no_param(i,2)}, no_param(i,1), no_param(i,2))
end

fprintf('
Biphasic cases')
fprintf('
Comp 1	Comp 2	i	j')
for i = 1:p-1
    fprintf('
%s 	%s 	%g 	%g', comps{biphasic(i,1)}, comps{biphasic(i,2)}, biphasic(i,1), biphasic(i,2))
end

fprintf('
'); toc
Appendix E: Micro fabrication protocols and masks

Project name: DRIE nitride reactor

Starting materials for micro fabricated packed beds:
1000 um thick, 6-inch Double Side Polished Silicon Wafer with 5000 A low-stress nitride from the VTR tube
1 mm thick, 6-inch Pyrex Wafer

Starting materials for micro fabricated packed beds:
650 um thick, 6-inch Double Side Polished Silicon Wafer with 5000 A low-stress nitride from the VTR tube
1 mm thick, 6-inch Pyrex Wafer

General process: DRIE etch of a wafer followed by a through etch from the back-side to provide inlet and outlet connections. Once the etching is complete, the nitride mask is removed and fresh nitride is deposited. A pyrex wafer is anodically bonded to the frontside to form the reactor. Individual devices are finally die-sawed

<table>
<thead>
<tr>
<th>FAC</th>
<th>MACHINE</th>
<th>ACTION</th>
<th>NOTES</th>
<th>CODE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TRL</td>
<td>Piranha clean before processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>AcidHood</td>
<td>Coat wafer with HMDS program 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>TRL</td>
<td>Spin Coat photoresist 10 µm AZ 9260 Bake at 95°C for 60 minutes</td>
<td>Static dispense, 60 s spread at 2000 RPM, 8 s spin at 3000 RPM</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>TRL</td>
<td>Expose resist for 15 seconds, 3 times with 15 sec interval</td>
<td>Mask 1</td>
<td></td>
</tr>
<tr>
<td>1.3</td>
<td>TRL</td>
<td>Development, 3 min Bake at 95°C for 30 minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4</td>
<td>TRL</td>
<td>Etch nitride</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pattern Nitride with RIE

DRIE - Step-1
<table>
<thead>
<tr>
<th>Step</th>
<th>TRL</th>
<th>Task Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8</td>
<td>AcidHood-1</td>
<td>Etch using JBETCH recipe for 400 µm, Piranha clean to remove photoresist, Approx rate ~2.5 µm/min</td>
</tr>
<tr>
<td>1.9</td>
<td>1</td>
<td>Photolithography for DRIE -step-2</td>
</tr>
<tr>
<td>2.1</td>
<td>HMDS</td>
<td>Coat wafer with HMDS program 3, Static dispense, 60 s spread at 2000 RPM, 8 s spin at 3000 RPM</td>
</tr>
<tr>
<td>2.2</td>
<td>coater</td>
<td>Spin Coating of photoresist 10 µm AZ 9260, Bake at 95°C for 60 minutes</td>
</tr>
<tr>
<td>2.3</td>
<td>prebake</td>
<td>Expose resist for 15 seconds, 3 times with 15 sec interval, Mask 2</td>
</tr>
<tr>
<td>2.4</td>
<td>EV1</td>
<td>Development, 3 min, Bake at 95°C for 30 minutes</td>
</tr>
<tr>
<td>2.5</td>
<td>photowet-1</td>
<td>Pattern Nitride with DRIE</td>
</tr>
<tr>
<td>2.6</td>
<td>postbake</td>
<td>Etch nitride</td>
</tr>
<tr>
<td>2.7</td>
<td>LAM490</td>
<td>DRIE-Step-2, Coat silicon handle wafer with thin resist in ring shape patterns, Handle wafer attachment, Attach handle wafer and bake for 30 minutes, Etch using JBETCH recipe for 250 µm, Through etch</td>
</tr>
<tr>
<td>2.8</td>
<td>coater</td>
<td>Acetone rinse to separate wafers, ~1 hr</td>
</tr>
<tr>
<td>2.9</td>
<td>prebake STS-2</td>
<td>Solvent Hood AcidHood-1, Piranha clean</td>
</tr>
<tr>
<td>2.10</td>
<td>Solvent</td>
<td>Asher AcidHood-1, O2 plasma, Post STS clean</td>
</tr>
<tr>
<td>2.11</td>
<td>Hood AcidHood-1</td>
<td>Piranha clean</td>
</tr>
<tr>
<td>2.12</td>
<td>1</td>
<td>Nitride Removal, Cone HF to remove all nitride, 1000 A per 20 min</td>
</tr>
<tr>
<td>2.13</td>
<td>Asher AcidHood-1</td>
<td></td>
</tr>
</tbody>
</table>
### Nitride Deposition

| 3.2 | TRL  | RCA    | VTR   | RCA clean
| 3.3 | ICL   |        |       | Deposit 5000 A low stress nitride

### Bonding and Die-Saw

| 4.1 | TRL  | 1      | AcidHood- | Piranha pyrex wafer and process wafer
| 4.2 | TRL  | EV501  |          | Bond silicon and pyrex wafers
| 4.3 | ICL  | Die-saw|          | Die-saw to get individual devices

1000 V at 450 C for 15 min
Packed bed microreactor front
Packed bed microreactor back
4-port continuous serpentine with LL separator front
4-port continuous serpentine with LL separator back
Appendix F: Engineering drawings

Packed bed reactor packaging chuck, bottom
Packed bed reactor packaging chuck, top

Note: Use of a wider window than indicated here is recommended.