Supporting Information

The Influence of Residence Time Distribution on Continuous-Flow Polymerization

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General methods and materials

Reagents

δ-valerolactone was dried over calcium hydride, distilled, and stored in a glove box prior to use. *N*-isopropylamide was recrystallized once from a 50/50 mixture of hexanes/toluene prior to use. *n*-butyl acrylate and *N,N*-dimethylacrylamide were passed through an alumina column in order to remove inhibitor prior to use. All other reagents were purchased and used without further purification.

Analysis

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker model DRX 400 MHz spectrometer with a solvent resonance as the internal standard (^{1}H NMR: CDCl$_3$ at 7.26 ppm or D$_2$O at 4.79 ppm). UV-Vis spectra were measured on a Gilson 151 UV/VIS Multilength Detector at 254 nm coupled with a Vapourtec R-series recorder.

Gel permeation chromatography (GPC) for poly(*N,N*-dimethylacrylamide) samples was performed on an Agilent 1260 Infinity separation module liquid chromatograph equipped with two Agilent Resipore Columns (PL1113-6300) maintained at 50 °C, and an Agilent 1260 RID G1362A refractive index detector at 50 °C. A solution of 0.1 wt% LiBr in dimethylformamide (DMF) was used as the mobile phase at a flow rate of 1.0 mL/min. Molecular weight and dispersity data are reported relative to poly(ethylene oxide) standards.

For all other polymer samples GPC analysis was performed on a Waters 2695 separations module liquid chromatograph equipped with either four Waters Styragel HR columns (WAT044225, WAT044231, WAT044237, and WAT054460) arranged in series or two Agilent Resipore columns (PL1113-6300) maintained at 35 °C, and a Waters 2414 refractive index detector at room temperature. Tetrahydrofuran was used as the mobile phase at a flow rate of 1.0 mL/min. Molecular weight and dispersity data are reported relative to polystyrene standards.

Viscosity measurements for polyethylene glycol-water solutions were taken on an ARES-G2 from TA instruments using a concentric cylinder and cup geometry. These solutions were prepared by dissolving polyethylene glycol (M_n = 20,000 g/mol) in water.

Flow geometries

Flow rates for all experiments were calculated by measuring the internal volume of the reactor tubing and dividing by the desired retention time. Listed below are the lengths of tubing used in each experiment.

Experiments	Tubing size	Tubing length	Reactor volume
UV-Vis measurements	0.02 in.	150 cm	304 μL
	0.03 in.	150 cm	684 μL
	0.04 in.	150 cm	1.22 mL
	0.063 in.	150 cm	2.92 mL
	0.093 in.	150 cm	6.57 mL
Poly(δ-valerolactone) polymerizations	0.02 in.	150 cm	304 μL
	0.03 in.	150 cm	684 μL
	0.04 in.	150 cm	1.22 mL
	0.04 in. Droplet	150 cm	1.22 mL
	0.063 in.	20 cm	390 μL
	0.093 in.	30 cm	1.31 mL
	0.093 in. Scale up	900 cm	39.44 mL
Poly (n-butyl acrylate) and poly(N-Isopropylacrylamide) polymerizations	0.04 in.	150 cm	1.22 mL
	0.093 in.	30 cm	1.31 mL
	0.093 in. Scale up	900 cm	39.44 mL
Poly(N,N-dimethylacrylamide) polymerizations	0.04 in.	150 cm	1.22 mL
	0.093 in.	30 cm	1.31 mL
	0.093 in. Scale up	180 cm	7.89 mL

Flow equipment

Flow tubing and connections were purchased from Upchurch Scientific (IDEX Health and Science). Syringe pumps and syringes were purchased from Harvard Apparatus. Luer-lock adapters were purchased to allow withdrawing reaction solution using standard needles (Idex Health and Science).
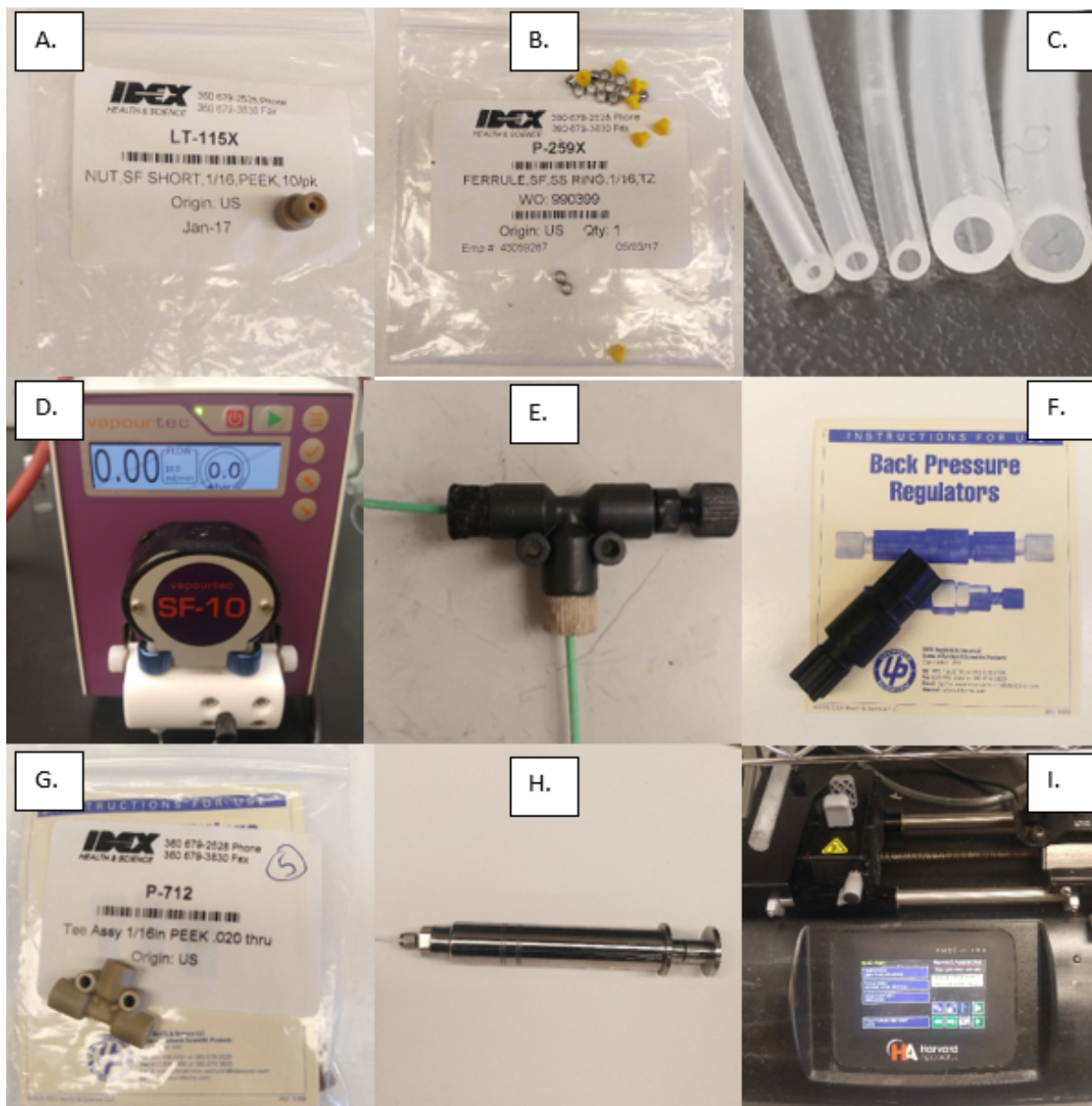

Figure S1. A. PEEK super-flangeless nut **B.** Yellow super-flangeless ferrule with corresponding stainless steel ferrule ring -- sold separately – larger sizes needed for 0.063 and 0.093 in. tubing. **C.** 0.02 in., 0.03 in., 0.04 in., 0.063 in., and 0.093 in. tubing **D.** Vapourtec SF-10 peristaltic pump **E.** Micrometering valve (part number p-445) **F.** back pressure regulator, 40 PSI (part number P-785) **G.** Static mixing Tee **H.** 20 mL stainless steel syringe **I.** Ph.D Ultra syringe pump
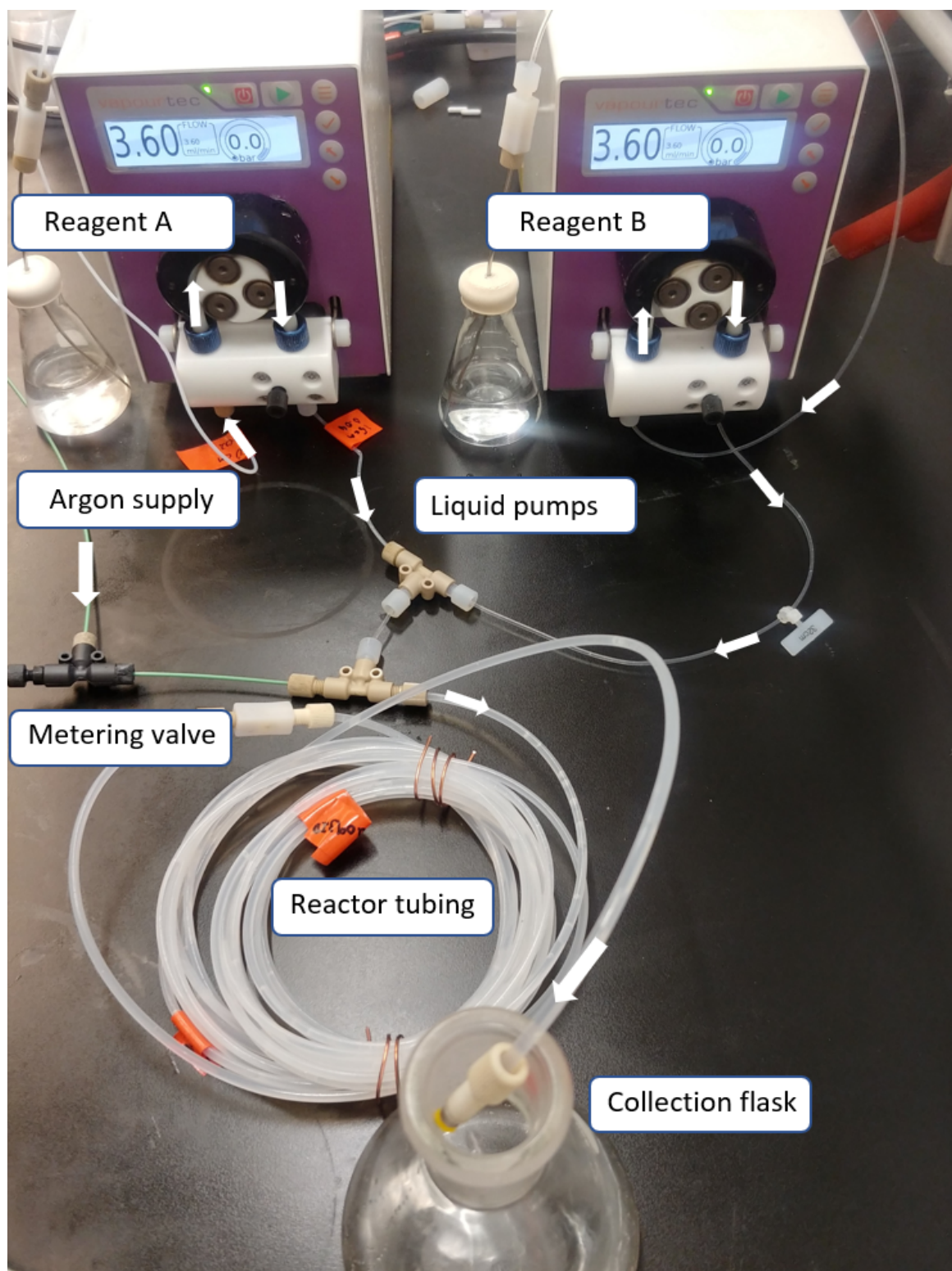
Figure S2. Reaction setup for the scaled-up synthesis of poly(δ-valerolactone). Useful protocol for how to set-up a flow system can be found at the following reference: Britton, J.; Jamison, T. F.; The assembly and use of continuous flow systems for chemical synthesis. *Nature Protocols.* **2018,** *12*, 2423-2446

Polymerization methodology

Poly(δ-valerolactone)

In the glove box using dry reagents and solvents, two solutions were prepared. The first was charged with 0.925 mL (10 mmol) of δ-valerolactone, 0.75 mL of DCM, and a stir bar. The second was charged with 1 mL of DCM, 4.5 mg (0.032 mmol) of triazabicyclodecene, and 10μL (0.080 mmol) of anhydrous 1-hexanol. To initiate the polymerization the two solutions were combined at room temperature and allowed to stir for 10 minutes before being quenched by addition of a small amount of acetic acid. At 100% conversion the target DP is 125 and the target M_n is 12,500.

For flow reactions the solutions were instead loaded into two different syringes that had been dried under vacuum overnight and brought into the glovebox. Outside of the glove box the syringe pumps were set to an identical flow rate with the total rate targeting a 10 minute retention time. A third pump containing an acetic acid/DCM solution was used to quench the reaction. To reach steady state, the pumps were run for 30 minutes (3 retention times) before collecting product.

For scale-up in droplet flow, solutions were prepared inside the glove box in two separate septum caped Erlenmeyer flasks. The peristaltic pumps were set to flow rates slightly lower than predicted for a 10 minute retention time. At first the peristaltic pumps pumped DCM through the system to allow manual adjustment of the argon flow rate until a 10 minute retention time was approximated by visually measuring the velocity of the air bubbles. Once a suitable retention time was estimated the peristaltic pumps began feeding from their respective monomer and catalyst/initiator solutions. When those solutions had been depleted the pumps were switched back to DCM to push the remaining volume of reaction solution through the reactor. During this experiment 100% of material was collected in a single vessel and then further analyzed via NMR and GPC.

Poly(*n*-butyl acrylate)

A single round bottom flask was charged with 28.7 mL (0.2 mol) of deinhibited *n*-butyl acrylate, 98.5 mg (0.6 mmol) of azobisisobutyronitrile, 254 mg (2 mmol) of 2-(2-carboxyethylsulfanylthiocarbonylsulfanyl)propionic acid and 71.3 mL of ethyl acetate. Argon was then bubbled through the solution for 60 minutes. At 100% conversion the target DP is 200 and the target M_n is 25,600 g/mol

For the batch reaction a 2 mL sample was transferred into a small vial pre-purged with Argon and equipped with a stirbar and gas-tight septa. The vial was allowed to stir in a 80°C heat bath for 30 minutes before being quenched by the addition of butylated hydroxytoluene and removal from heat.

For flow reactions the desired length of tubing was submerged in a 80°C heat bath before the solution was loaded into a syringe and the flow rate of the syringe pump was set to target a 30 minute retention time. To reach steady state, the pump was run for 90 minutes (3 retention

times) before product was collected in a vial containing a small amount of butylated hydroxytoluene.

For scale-up in droplet flow, the desired length of tubing was submerged in a 80°C heat bath before the peristaltic pump was set to flow rate slightly lower than predicted for a 30 minute retention time. At first ethyl acetate was pumped through the system to allow manual adjustment of the argon flow rate until a 30 minute retention time was approximated by visually measuring the velocity of the air bubbles. Once a suitable retention time was estimated the peristaltic pump began feeding from reaction solution. When that solution had been depleted the pumps were switched back to ethyl acetate to push the remaining volume of reaction solution through the reactor. During this experiment 100% of material was collected in a single vessel and then further analyzed via NMR and GPC.

Poly(*N*-isopropylacrylamide)

A 100 mL volumetric flask was charged with 22.6 g (0.2 mol) of *N*-isopropylacrylamide, 98.5 mg azobisisobutyronitrile, and 254 mg (2 mmol) of 2-(2-carboxyethylsulfanylthiocarbonylsulfanyl)propionic acid. Ethyl acetate was added until the total solution volume reached 100 mL. Argon was then bubbled through the solution for 60 minutes. At 100% conversion the target DP is 200 and the target M_n is 22,600 g/mol. For the batch reaction a 2 mL sample was transferred into a small vial pre-purged with Argon and equipped with a stirbar and gas-tight septa. The vial was allowed to stir in a 100°C heat bath for five minutes before being quenched by the addition of butylated hydroxytoluene and removal from heat.

For flow reactions the desired length of tubing was submerged in a 100°C heat bath before the solution was loaded into a syringe and the flow rate of the syringe pump was set to target a 5 minute retention time. To reach steady state, the pump was run for 15 minutes (3 retention times) before product was collected in a vial containing a small amount of butylated hydroxytoluene.

For scale-up in droplet flow, the desired length of tubing was submerged in a 100°C heat bath before the peristaltic pump was set to a flow rate slightly lower than predicted for a 5 minute retention time. At first ethyl acetate was pumped through the system to allow manual adjustment of the argon flow rate until a 5 minute retention time was approximated by visually measuring the velocity of the air bubbles. Once a suitable retention time was estimated the peristaltic pumps began feeding from reaction solution. When those solutions had been depleted the pumps were switched back to ethyl acetate to push the remaining volume of reaction solution through the reactor. During this experiment 100% of material was collected in a single vessel and then further analyzed via NMR and GPC.

Poly(*N,N*-dimethylacrylamide)

A single vial was charged with 6.15 mL (0.060 mol) of deinhibited *N,N*-dimethylacrylamide, 9.6 mg (0.030 mmol) of 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (VA-044), 35.7 mg (0.15 mmol) of 2-(butylthiocarbonothioylthio)propanoic acid, 19.2 mL deionized water, and

4.65 mL 1,4-dioxane. The solution was not degassed prior to reacting. At 100% conversion, the target DP is 400 and the target M_n is 39,700 g/mol. For the batch reaction a 2 mL sample was transferred into a small vial pre-purged with Argon and equipped with a gas-tight septa. The vial was allowed to stir in a 100°C heat bath for 1 minute before being removal from heat and exposed to air to allow quenching.

For the preheated batch reaction, the initiator was separately dissolved at room temperature in 0.2 mL of deionized water and injected into monomer/CTA solution that had been submerged in a 100°C heat bath for two minutes.

For flow reactions the desired length of tubing was submerged in a 100°C heat bath before the solution was loaded into a syringe and the flow rate of the syringe pump was set to target a 1 minute retention time. To reach steady state, the pump was run for 3 minutes (3 retention times) before product was collected in a vial open to air.

For scale-up in droplet flow, the desired length of tubing was submerged in a 100°C heat bath before the peristaltic pump was set to a flow rate slightly lower than predicted for a 1 minute retention time. At first the peristaltic pumps pumped deionized water through the system to allow manual adjustment of the argon flow rate until a 1 minute retention time was approximated by visually measuring the velocity of the air bubbles. Once a suitable retention time was estimated the peristaltic pump began feeding from reaction solution.

Polymerization data not included in the main text

Poly(*N*-isopropylacrylamide)

Reactor geometry	M_n (g/mol)	Đ	Conversion (%)
Batch (2 mL scale)	10900	1.24	79
Flow (0.04 in. tubing)	10800	1.26	75
Flow (0.093 in. tubing)	8900	1.28	67
Droplet (0.093 in. tubing)	9800	1.13	67

The polymerization of *N*-isopropylacrylamide in droplet flow achieved a narrower Đ than batch. We hypothesize that this is due to the loss of control in batch at these higher temperatures. When combined with a back-pressure regulator, the polymerization in flow is better able to maintain control at temperatures well above the solvent's boiling point.

Poly(*N,N*-dimethylacrylamide)
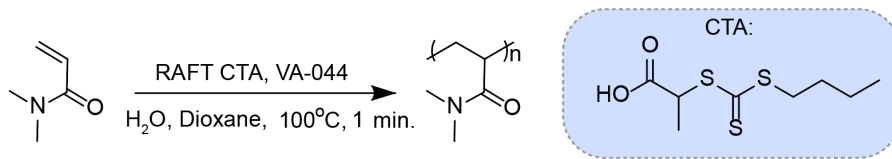
Reactor geometry	M_n (g/mol)	Đ	Conversion (%)
Batch (2 mL scale)	-	-	6
Pre-heated (2 mL scale)	13800	1.14	89
Flow (0.04 in. tubing)	10200	1.38	64
Flow (0.093 in. tubing)	6700	1.53	38
Droplet (0.093 in. tubing)	12100	1.26	82

For this reaction the rate of heat transfer and mixing played a large role in the conversion of the product. These variables had a larger influence than for other reactions because of the short reaction time, the high specific heat of water, and the need for rapid mixing to facilitate simultaneous initiation. For these reasons it was difficult to discern if the drastically different conversions are due to RTD effects or different rates of mixing and heat transfer in each geometry.

Sample residence time distribution visualization

Raw UV-vis data was collected from the recorder as a number of discrete data points.
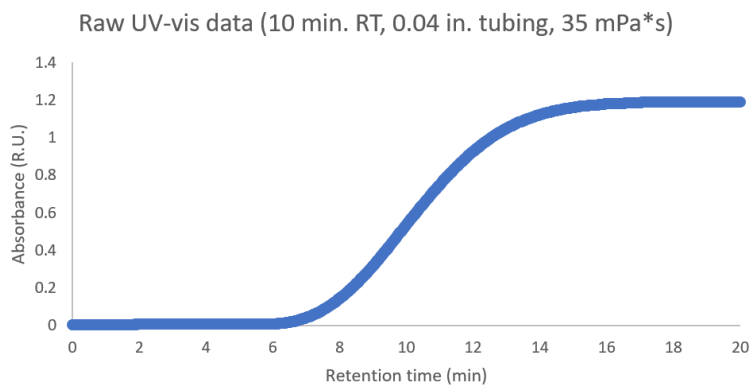
The slope cannot be directly found using the first derivative because the raw data is a number of discrete points rather than a continuous function. Instead slope of each data point is measured by the ratio of change in y-axis and change in x-axis. The instrument makes measurements every second so the slope is calculated from the change in absorption per every one second period.

**Slope at 1 second intervals (10 min. RT, 0.04 in. tubing, 35 mPa*s)**
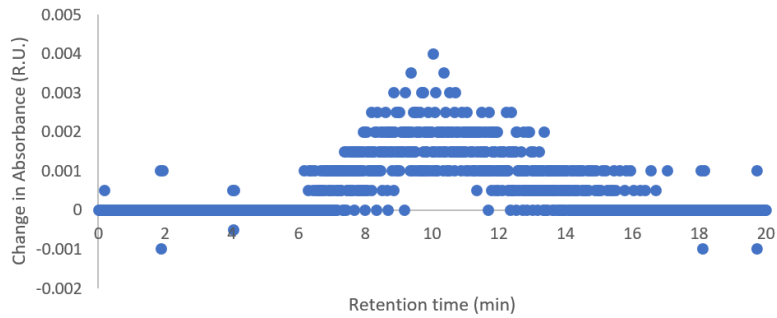
As seen above, the data doesn't represent the RTD in an easy to interpret manner. This is due to the change in absorbance per second being very small. To fix this problem multiple data points are summed together, resulting in the change in absorbance per 5 seconds, 10 seconds or longer.

Slope at 5 second intervals (10 min. RT, 0.04 in. tubing, 35 mPa*s)
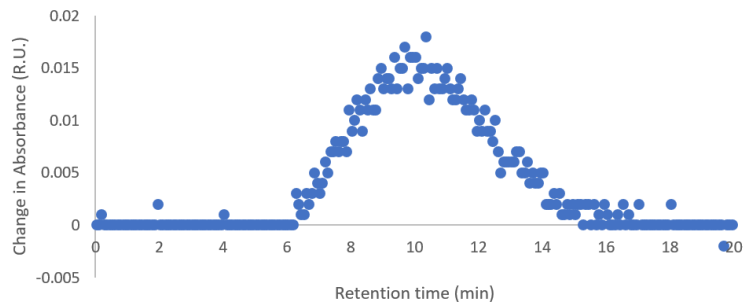
**Slope at 25 second intervals (10 min. RT, 0.04 in. tubing, 35 mPa*s)**
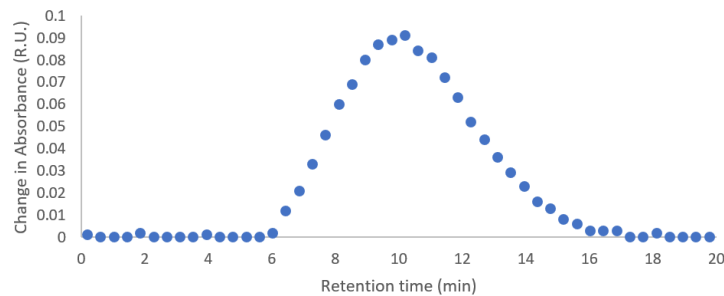
Once a good interval for averaging the slopes is determined we normalize the data on both the x and y axis. Normalizing the x-axis requires first finding the mean retention time. For a symmetric curve, is as simple as finding the time point that corresponds to half of the total change in absorbance.

Raw UV-vis data (10 min. RT, 0.04 in. tubing, 35 mPa*s)
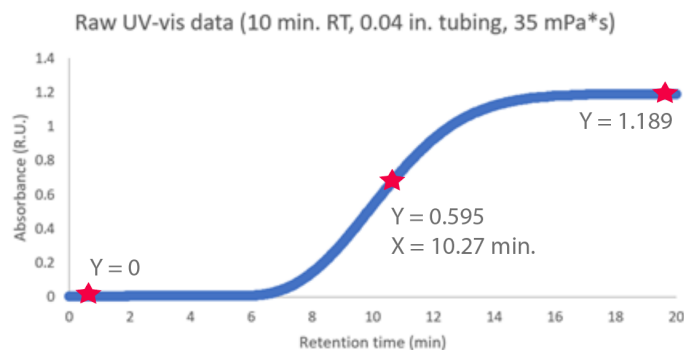
In this experiment the mean residence time was found to be 10.27 minutes. This is higher than the 10-minute predicted residence time due to dead volume between the reactor and the detector. In order to normalize the RTD, the X-axis was divided by the mean residence time and the Y-axis was divided such that the total area under the curve was equal to one. This allows the direct comparison of different RTD's even at different residence times or using different numbers of averaged points.

Affect of droplet flow on RTD

Affect of Droplet Flow on RTD (10 min RT, 0.04 ID Tubing)
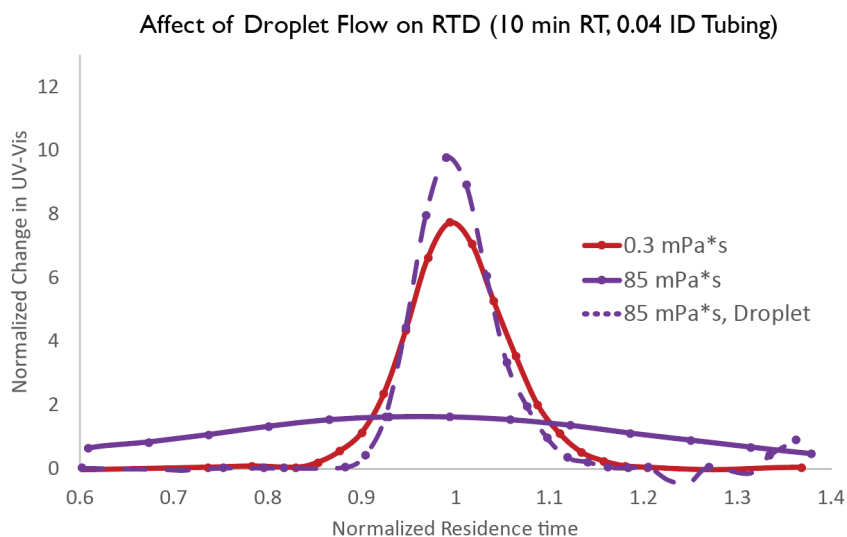
The utilization of droplet flow was shown to drastically decrease the observed residence time distribution. In this representative series, droplet flow was shown to improve the RTD of the most viscous sample tested (which even surpassed the least viscous sample). However, under these conditions a distribution of reaction times is still observed. We hypothesize this is due to cross contamination of droplets originating from the thin film of liquid between droplets that has adhered to the fluoropolymer tubing.

General tips for working with gas flow

Incorporation of the gaseous phase into a flow reactor increases the complexity of the reaction and thus, we have included some general tips for readers who are new to working with the gas phase in microfluidic reactions.

Introducing the gas phase into the flow reactor

Gas is introduced into the reactor using a pressurized gas cylinder equipped with a standard pressure regulator. Connecting the regulator to the flow system can be achieved using a Swagelok connector that directly attaches to $1/8^{th}$ in tubing. Downstream of the pressure regulator is a simple metering valve that can be manually adjusted to control the flow rate of the gaseous phase. The rate at which gas is delivered is proportional to how open the metering valve is as well as the pressure differential across the valve. We found it easier to precisely control the flow rate when the pressure of the gas regulator was set slightly higher than the back-pressure regulator attached at the end of the flow reactor. The liquid and gaseous flows are then combined together using a T-mixer. The size of the argon bubbles introduced into the system can be tuned by changing the orifice size of the T-mixer where the liquid and gaseous phase meet. The smaller the I.D. of the T-mixer, the smaller and more frequent the resulting gaseous bubbles.

Controlling retention time using a gas-liquid biphasic system

Adding gas into a system introduces significant complications when trying to precisely target retention times due to its compressible nature. Often in liquid-only flow reactors retention times are calculated using the volumetric flow rate / total reactor volume. Due to the compressible nature of gas, the volume gas displaces within the reactor is affected by several factors including *i.* temperature, *ii.* System pressure and pressure drop, *iii.* Gas solubility in the liquid phase, and *iv.* Gaseous diffusion through the flow tubing. Rather than use a volumetric measurement to measure retention time, visually measuring the speed of the travelling droplets within the flow tubing can be a viable alternative. Using this method, an approximation of the retention time can be calculated from the speed of the droplet / the total reactor length.

Other considerations

Within these gas-liquid biphasic systems, the liquid is the continuous phase, meaning that a thin film of liquid is constantly wetting polymer tubing and connects all liquid slugs within a system. This thin film leads to small amounts of cross contamination between a liquid slug and the slugs immediately following it.

To increase the reproducibility and precision for introducing gas into the system, the simple metering valve can be swapped out for a mass flow controller. A mass flow controller precisely doses in a mass flow rate of gas, however, it should be noted that the same problems still persist when trying to target retention times as the mass flow controller has no knowledge of reaction conditions downstream.