Supplementary Material

Characterization of Dispersion Effects on Reaction Optimization and Scale-Up for a Packed Bed Flow Hydrogenation Reactor

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Dispersion Characterization Calculations. Using the bolus injection approach described in the experimental, both mean residence time and variance of a bolus inside the reactor can be measured to approximate both the reactor hold up-volume and the dispersion caused by the reactor. Rigorous models exist in chemical engineering texts for the determination residence times and dispersion (so called residence time distribution, RTD, models) which are outside the scope of our work. As a substitute to assess the approximate volume and dispersion of the H-Cube reactor, we instead choose to treat the system as a classic HPLC where simple models to evaluate the dispersion have been well described. In brief, by fitting a Gaussian distribution to the measured dispersion profiles (Figure S2) we can determine both the reactor residence time(R_t) and the variance (σ^2) of the profile. Finally, we can determine the reactor volume for non-porous catalysts using the simple relationship $V = F \cdot R_t$ where V is the reactor volume and F is the volumetric flow rate.

The reactor residence time and variance are both additive components allowing us to break the overall H-Cube reactor into various zones to characterize where the most significant volume and dispersion are occurring. For simplicity, the H-Cube zones are defined as the pre-heating block fluidic components, the H-Cube heating block, the CatCart and the post-block zones, as shown in Figure S1. We can then write the overall reactor residence time model as:

$$Rt_{H-Cube} = Rt_{Pre-Block} + Rt_{Heater} + Rt_{Cart} + Rt_{Post-Block} + Rt_{ext} \quad (1)$$

Where Rt_{ext} are the external contributions from the injector, detector and associated tubing without the H-Cube present. The design of the H-Cube does not easily allow separate measurement of the pre-and-post block zones therefore those terms can be combined as a single fluidics measure. Equation 1 can then combined and written as:

$$Rt_{H-Cube} = Rt_{ext} + Rt_{fluidics} + Rt_{Heater} + Rt_{Cart} \quad (2)$$

Where $Rt_{fluidics}$ now represents both the pre- and-post block zones and Rt_{ext} represents all of the measurement system sources of volume. We can similarly write the reactor contributions for variance as:

$$\sigma_{H-Cube}^2 = \sigma_{ext}^2 + \sigma_{fluidics}^2 + \sigma_{heater}^2 + \sigma_{Cart}^2 \quad (3)$$

Equations 2 and 3 allow the determination of the individual contributions of each component of the reactor. Ideally, each component would be measured independent of the others in a single experiment and then combined to compare against the overall reactor dispersion. Unfortunately, the fluidic design of the H-Cube prevents the measurement of the contributions of the heater block directly. It is possible, however, to perform measurements of both the CatCart independent of the H-Cube and the H-Cube fluidic components disconnected from the heater block and CatCart. By measuring the values σ_{H-Cube}^2, $\sigma_{fluidics}^2$, and σ_{Cart}^2 (and similar Rt values) we can then solve for the contribution of the heater block itself using equations 2 and 3. Other groups have used a similar approach for characterization of gas-liquid dispersion.[12]

The contributions of the CatCart zone were determined directly using a QuartzCart and external CatCart Holder provided by ThalesNano since the Quartz packing material is non-porous and will have minimal adsorption effects which would artificially add to the measured dispersion. Fluidic dispersion measurements were carried out by plumbing the H-Cube bubble detector into the outlet pressure sensor (detailed discussion of hardware can be found in[1c, 7]), bypassing both the heater block and integrated holder. Plumbing the entire system with the same QuartzCart then allowed for the overall measurement of the reactor. The final calculations can then be written as:

$$\sigma_{H-Cube}^2 = \sigma_{H-Cube,meas}^2 - \sigma_{ext}^2$$
$$\sigma_{fluidics}^2 = \sigma_{fluidics,meas}^2 - \sigma_{ext}^2$$
$$\sigma_{Cart}^2 = \sigma_{cart,meas}^2 - \sigma_{ext}^2$$
$$\sigma_{heater}^2 = \sigma_{H-Cube}^2 - \sigma_{fluidics}^2 - \sigma_{Cart}^2 \quad (4)$$

with a similar set of equations for determining the *Rt* where the final values are determined by subtracting the external contributions from the actual measured value.

Using this final set of equations, the variance and mean residence time at a variety of flow rates can then be determined. While the impact of flow rate over a narrow region should be negligent, final measurements were still conducted at 0.5, 1 and 2ml/min. Example dispersion profiles are shown in Figure S2 for 0.5ml/min. Final results are summarized in Table S1.

Micro Cartridge Steady-State Profiling. As a potential solution to low-volume reactions, the vendor also provides a Micro Cartridge design. When compared to a standard 4mm id inert CatCart, the Micro is design with a 1mm id and approximately 16 fold less volume. Since the id and volume of the cartridge will have a direct impact on the overall dispersion, it was theorized that a micro cartridge might improve the overall %SS for lower volume injections. Results are shown in Figure S3. While figure S3B does show that the volume of the Micro cartridge is lower (indicated by the earlier elution time), the overall dispersion is similar. This is not too surprising given that the macro cartridge itself only contributes <15% to the overall dispersion (see Table S1) so while the Micro cartridge is an improvement, the H-Cube dispersion itself still dominates. Figure S3A shows no improvement in the amount of material at SS for any injection volume. This leads us to conclude the that the Micro cartridge may have advantages for certain chemistries where lower amounts of catalyst are beneficial, but appears to have little advantage for small-scale injections due to the dispersion already associated with the reactor.
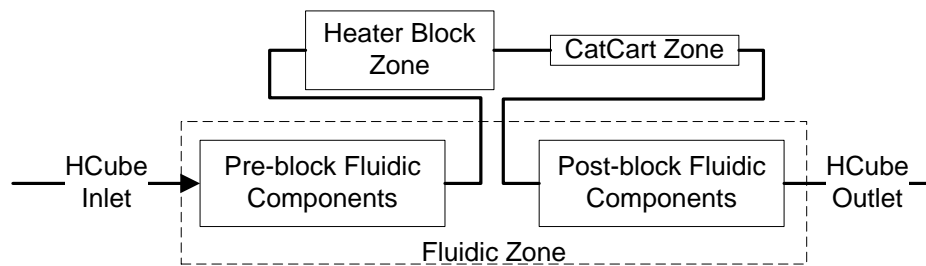
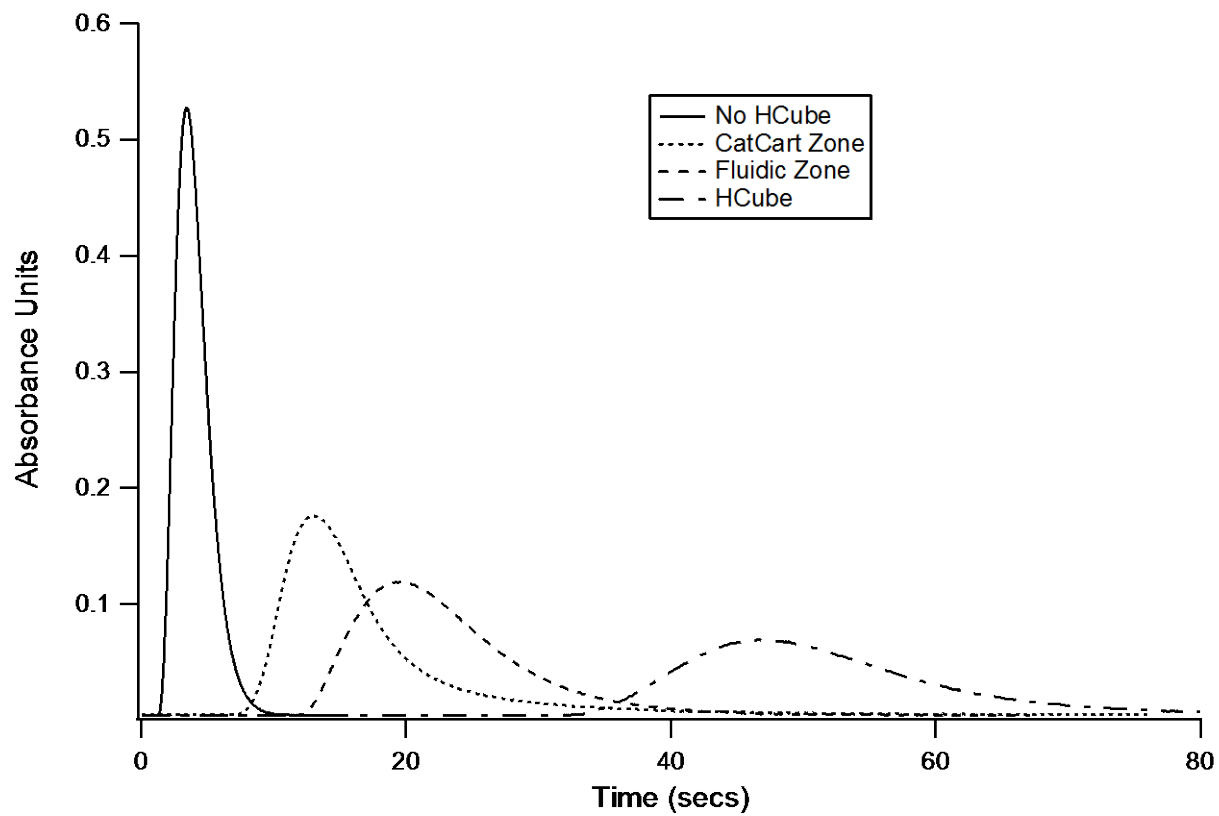**Figure S1:** Schematic of dispersion zones modeled for H-Cube®.

Figure S2: Dispersion profiles for CatCart Zone (with 30mm inert CatCart),Fluidic Zone and full H-Cube®. All measurements were 5μl plug injections of Caffeine at 0.5ml/min of Methanol.
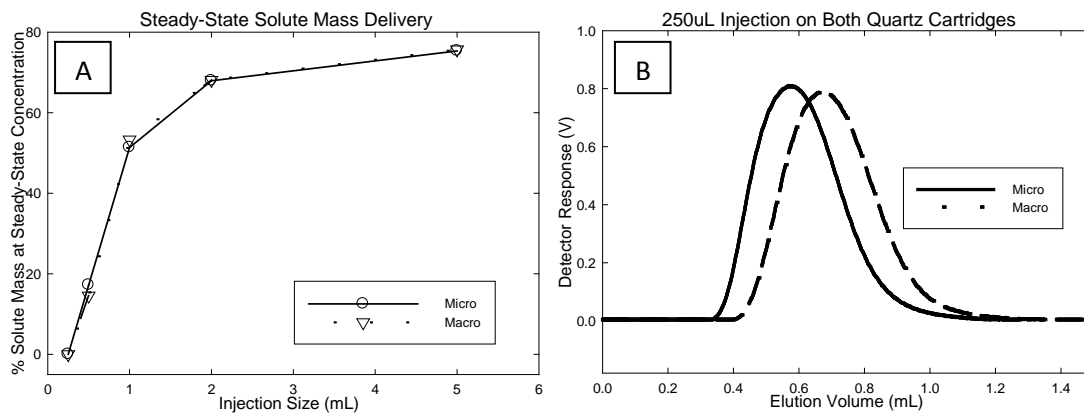
Figure S3: Comparison of Micro and CatCart Dispersion. Plot A is %SS while plot B is dispersion profile. Both are collected for 50mM caffeine at 1ml/min.

Table S1a: 0.5ml/min

Zone	Volume (µl)	% of Volume Contribution	Variance (sec^2)	% of Variance Contribution
Fluidics	144 ± 4	38%	22.1	36%
Heater	146 ± 4	39%	30.5	50%
CatCart	86 ± 3	23%	8.4	14%
H-Cube®	376 ± 11	100%	61.0	100%

Table S1b: 1ml/min

Zone	Volume (µl)	% of Volume Contribution	Variance (sec^2)	% of Variance Contribution
Fluidics	136 ± 3	37%	5.5	34%
Heater	151 ± 5	41%	8.4	52%
CatCart	84 ± 3	23%	2.4	15%
H-Cube®	371 ± 10	100%	16.3	100%

Table S1c: 2ml/min

Zone	Volume (µl)	% of Volume Contribution	Variance (sec^2)	% of Variance Contribution
Fluidics	146 ± 4	38%	1.4	37%
Heater	156 ± 4	40%	1.9	50%
CatCart	83 ± 3	22%	0.5	13%
H-Cube®	382 ± 12	100%	61.0	100%