Supporting Information

Model-Based Design of Transient Flow Experiments for the Identification of Kinetic Parameters

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1. Modelling a Transient Plug Flow Reactor as a Batch Reactor

For a transient Plug Flow Reactor (PFR) where the flowrate is ramped while holding all other experimental variables constant, the experiment is equivalent to running a single batch reactor as shown in Figure S1 below. In Figure S1a, the experimental data for the transient PFR is shown, including the flowrate, temperature and feed concentration profiles and the HPLC measured reactor outlet concentrations, which are collected at 7 min intervals. This reactor can also be modelled as a batch reactor by converting the measurement time of each data point, $t_{M,i}$, in Figure S1a, into the equivalent reaction time τ_i in Figure S1b by using Eqs 11-12 in the main paper.

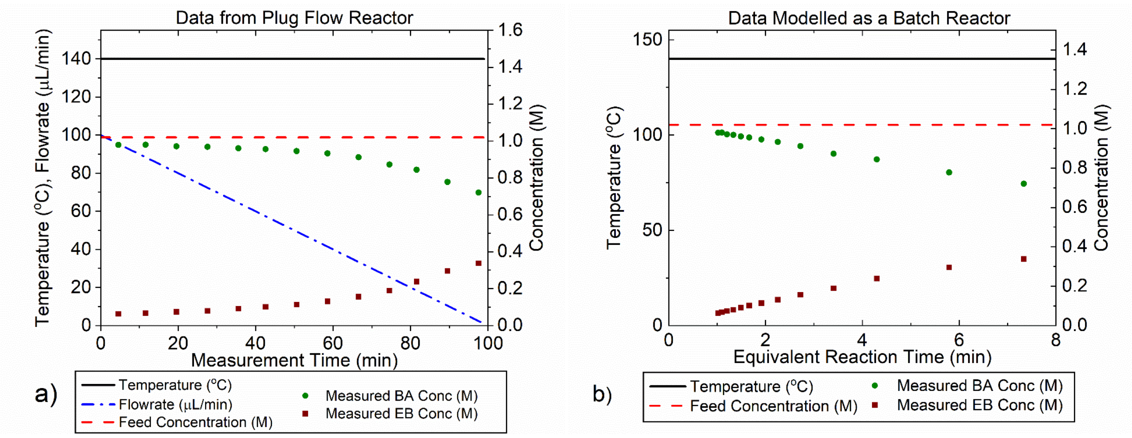

Figure S1. Data from the PFR when flowrate is ramped and all other variables are held constant a), which can then be modelled as a hypothetical batch reactor b). BA Conc is benzoic acid concentration, EB Conc is ethyl benzoate concentration, measurement time is the time the sample was measured by the HPLC and equivalent reaction time is the time each sample spent in the reactor.

For a transient Plug Flow Reactor (PFR) where flowrate and a second variable such as temperature are ramped simultaneously, each data point collected by the transient PFR can be modelled as a different hypothetical batch reactor, as shown in Figure S2. A single transient flow experiment is equivalent to running multiple batch reactor experiments, where each batch reactor provides a single measurement. As the transient experiment progresses the temperature is continuously changing, therefore the first "batch reactor" and the last "batch reactor" will have experienced different temperature profiles, and hence they cannot be modelled as the same batch reactor. Because of this, each data point is viewed as a different batch reactor with a ramping temperature profile as shown in Figure S2b, c and d. The measurement time of each data point, $t_{M,i}$, in Figure S2a, is converted into the equivalent reaction time τ_i in Figure S2b, c and d, by using Eqs 11-12 in the main paper. The initial temperature for each hypothetical batch reactor $T_{0,i}$, (the temperature at 0 min equivalent reaction time in Figure S2b, c and d) is calculated using Eq 9 in the main paper. The temperature of each hypothetical batch reactor is then ramped down from its initial temperature $T_{0,i}$, at the temperature ramp rate α_T.

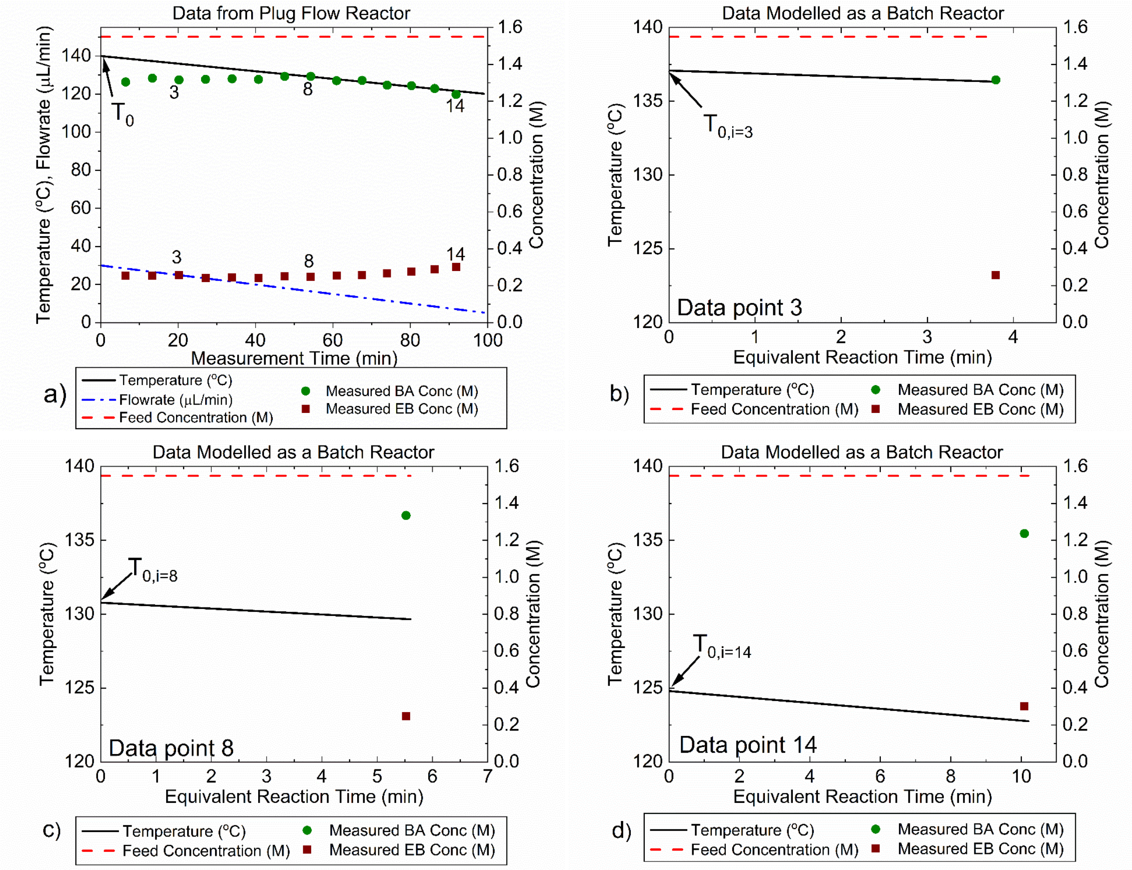

Figure S2. Data from the PFR when flowrate and temperature are ramped simultaneously, while feed concentration is held constant a), which can then be modelled as a series of hypothetical batch reactors shown for the 3rd, 8th and 14th data points in b) c) and d). BA Conc is benzoic acid concentration, EB Conc is ethyl benzoate concentration, measurement time is the time the sample was measured by the HPLC and equivalent reaction time is the time that each sample spent in the reactor.

2. Sensitivity of MBDoE to the Initial Guess of Kinetic Parameter Values

In order to test the sensitivity of the transient MBDoE designs to the values of the initial guess for the kinetic parameters *KP1* and *KP2*, the MBDoE design procedure was repeated 4 times with poor guesses for the parameter values. These 4 initial guesses were chosen to span over reasonable ranges of the kinetic parameters (corresponding to 60-110 kJ/mol for the activation energy and $3.95*10^4$ to $1.17*10^{11}$ s^{-1} for the pre-exponential factor). The 4 initial guesses are shown in Table S1 and Figure S3, where they can be compared against the initial guess that were used in the main paper. The confidence ellipsoid for the factorial estimates is also included to provide a scale to appreciate how poor the initial guesses are. The sensitivity of MBDoE to the initial guess is tested with these parameter values for both Ramp F and Ramp FT experiments.

Table S1. Initial guesses for the kinetic parameter values used to test the sensitivity of MBDoE to the initial parameter estimates (both Ramp F and Ramp FT scenarios).

Parameter Set	KP1	KP2	k_0 (s^{-1})	E_A (J/mol)	k at 100°C ($*10^5$ s^{-1})	k at 120°C ($*10^5$ s^{-1})	k at 140°C ($*10^5$ s^{-1})
Factorial Estimates	9.12	7.98	1.17E+07	79,800	0.78	2.88	9.40
A	8.5	6.0	3.95E+04	60,000	1.58	4.21	10.25
B	9.5	11	1.17E+11	110,000	0.47	2.84	14.50
C	8.5	10	1.32E+10	100,000	1.33	6.85	30.11
D	9.5	7.0	3.49E+05	70,000	0.56	1.75	4.94

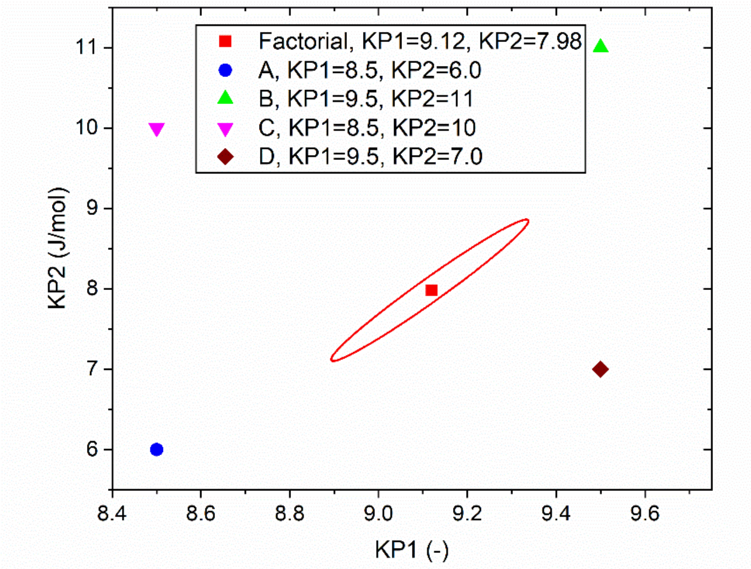

Figure S3. Initial guesses for the kinetic parameter values used to test the sensitivity of MBDoE to the initial parameter estimates.

As can be observed in Figure S4a and Figure S5a, the design of the flowrate profiles for MBDoE designed Ramp F experiments were similar regardless of the initial guess of the parameter values. In all cases the MBDoE designed flowrate was low, whereas the intuitively designed experiment from the previously published work had a large flowrate varying from 100 to 1 µL/min. The value of the feed concentration was always 1.55 M regardless of the initial parameter estimate. Additionally, the fixed temperature value designed by MBDoE was not very sensitive to the initial parameter guess, as all the temperature profiles designed for the second Ramp F experiment were almost identical, as shown in Figure S5b, and many of the temperature profiles for the first Ramp F experiment also were similar, as shown in Figure S4b.

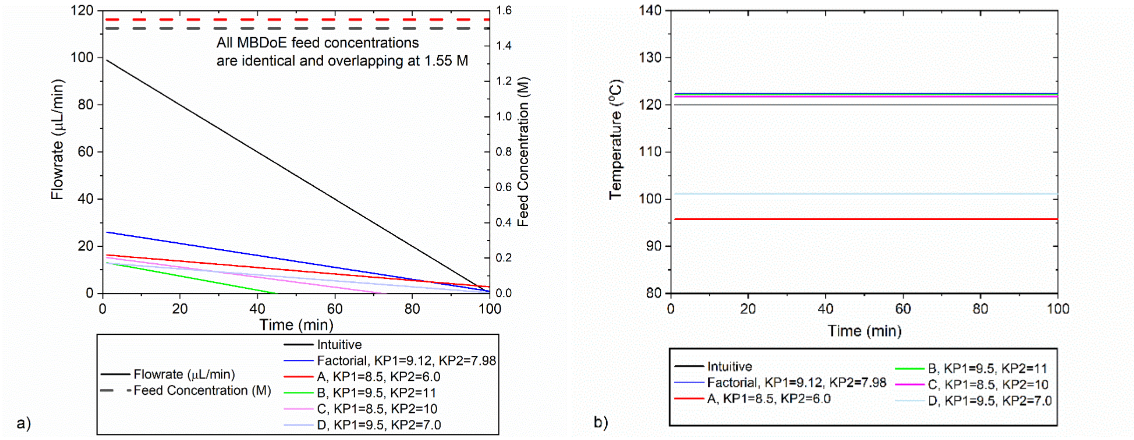

Figure S4. a) Flowrate and feed concentration profiles, b) Temperature profiles, for the first Ramp F experiment when designed intuitively (black)[1] and when designed by MBDoE using different initial guesses for the kinetic parameter values.

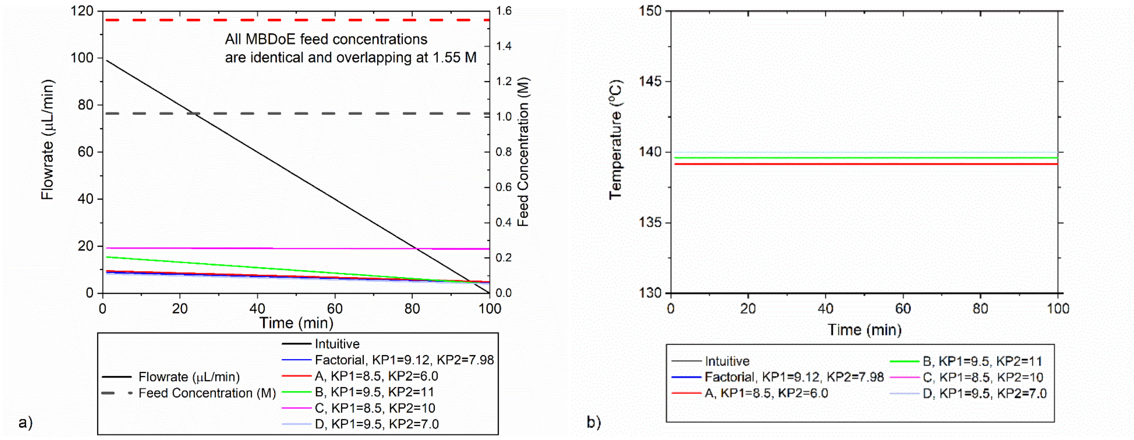

Figure S5. a) Flowrate and feed concentration profiles, b) Temperature profiles, for the second Ramp F experiment when designed intuitively (black)[1] and when designed by MBDoE using different initial guesses for the kinetic parameter values.

In order to quantify how effective these designs were for precise parameter estimation, the expected Fisher Information matrix for each experimental design was calculated by Eq 20 from the main paper, using what is believed to be the correct parameter estimate values of *KP1* = 9.12 and *KP2* = 7.98. The inverse of the expected Fisher Information matrix gives the expected covariance matrix, from which 95% confidence ellipsoids are obtained (since all confidence ellipsoids were generated with the same parameters, the difference in the ellipsoids is entirely due to the differences in the experimental design). Therefore, it is possible to predict the 95% confidence ellipsoids for these designs without having to actually conduct the experiments. Figure S6 shows that in all cases the confidence ellipsoids of the MBDoE designs are similar in size and are always significantly smaller than the intuitively designed experiment. This demonstrates that for the Ramp F scenario of this case study, the MBDoE is not sensitive to the values of the initial parameter guesses.

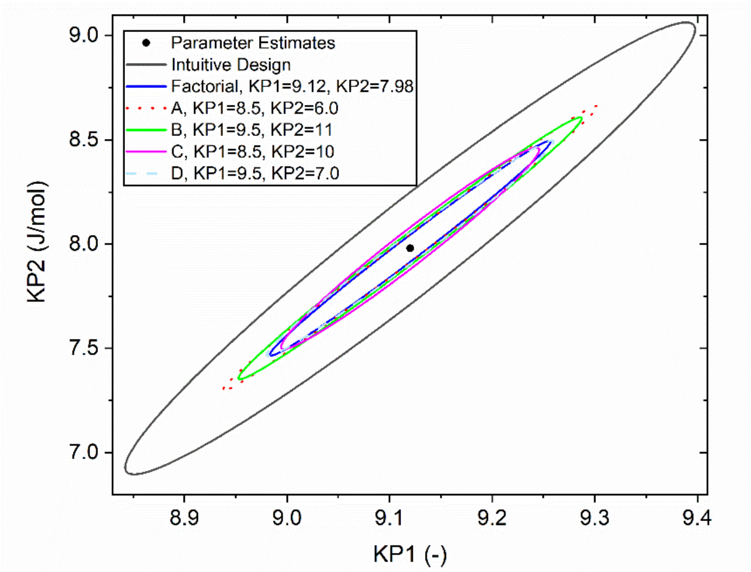

Figure S6. 95% Confidence ellipsoids comparing the statistical certainty of the kinetic parameters *KP1* and *KP2* for the Ramp F experiments designed intuitively (black)[1] and by MBDoE using different initial guesses for the kinetic parameter values.

The same procedure was repeated for the Ramp FT experiments. Figure S7a and b show that the design profile of MBDoE experiments is not very sensitive to the initial guess of the kinetic parameter values and that in all cases a low flowrate profile is designed which is different from the intuitively designed flowrate profile. The MBDoE temperature profiles were all quite similar regardless of the initial guess for the kinetic parameter values and the MBDoE feed concentration was always identical for all MBDoE designs.

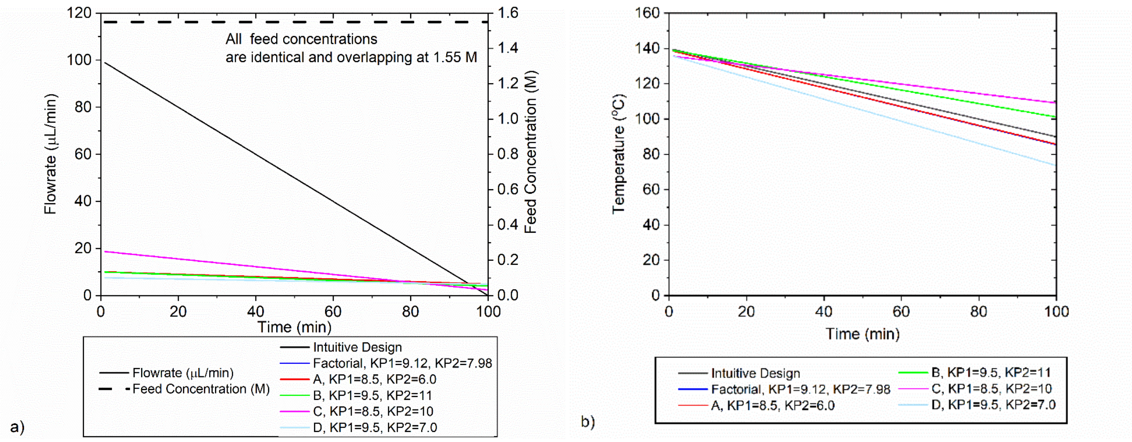

Figure S7. a) Flowrate and feed concentration profiles, b) Temperature profiles, for the Ramp FT experiments when designed intuitively (black)[1] and when designed by MBDoE using different initial guesses for the kinetic parameter values.

This demonstrates that the MBDoE designs which were created using the poor initial parameter estimates were still good designs and significantly superior than the intuitively designed experiment, as shown by the confidence ellipsoids in Figure S8. For this case study, MBDoE is not very sensitive to the initial parameter guess, and therefore it is a valuable technique even in the case of low certainty in the initial parameter guess. However, it would always be beneficial to use as reliable an initial estimate as possible. Hence, sequential design of transient MBDoE experiments would be the best strategy, as the initial estimate improves with each experiment.

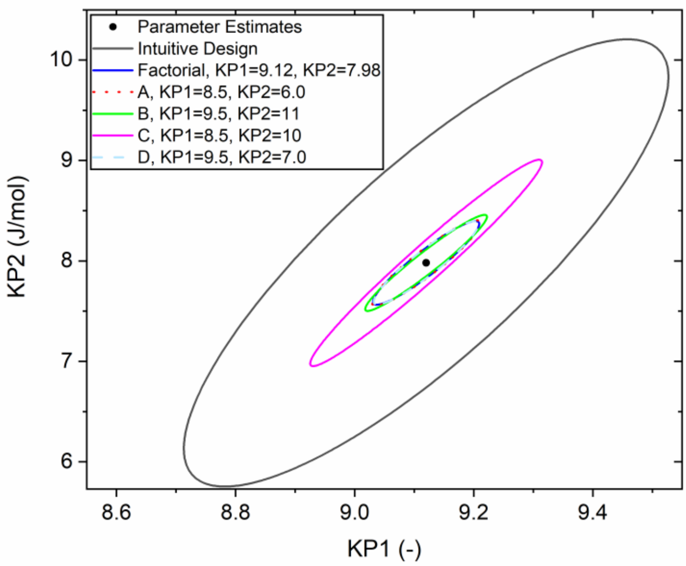

Figure S8. 95% Confidence ellipsoids comparing the statistical certainty of the kinetic parameters *KP1* and *KP2* for the Ramp FT experiments designed intuitively (black)[1] and by MBDoE using different initial guesses for the kinetic parameter values.

3. Data from Experimental Measurements

The values of the measured outlet concentrations along with their measurement time and equivalent residence time are reported in Table S2, Table S3 and Table S4 and shown graphically in Figure S9a and b, and Figure S10 for the three experiments conducted in this work.

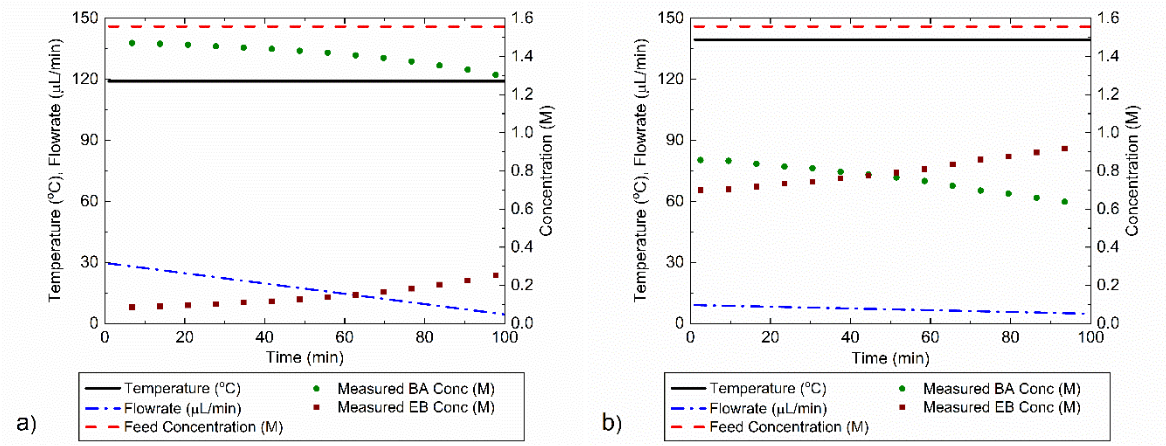

Figure S9. Control variable profiles and measured outlet concentrations of BA (benzoic acid) and EB (ethyl benzoate) for a) the 1st and b) 2nd MBDoE designed flowrate ramp experiment (Ramp F), while keeping temperature and benzoic acid inlet concentration constant.

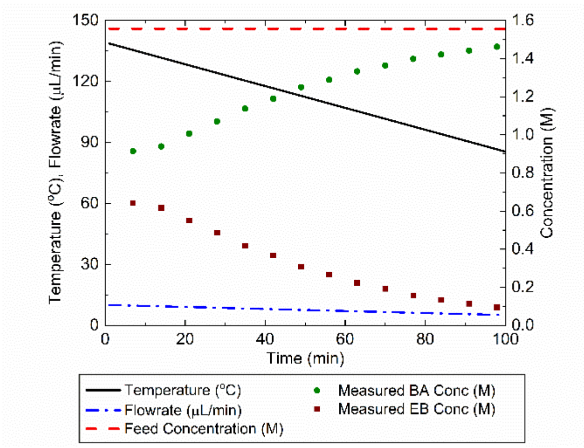

Figure S10. Control variable profiles and measured outlet concentrations of BA (benzoic acid) and EB (ethyl benzoate) for the MBDoE designed experiment where flowrate and temperature were ramped simultaneously (Ramp FT), while keeping benzoic acid inlet concentration constant.

Table S2. Time each sample was measured, left and entered the reactor and corresponding reaction time, along with conversion and outlet concentrations of benzoic acid and ethyl benzoate for the first MBDoE Ramp F experiment. The initial flowrate was 29.8 μL/min, the flowrate was ramped down at a rate of 0.253 μL/min^2, while the temperature was held constant at 119 °C and the feed concentration was 1.56 M.

$t_{M,i}$ Time the sample was measured	$t_{In,i}$ Time the sample entered the reactor	$t_{L,i}$ Time the sample left the reactor	τ_i Sample reaction time	X Conversion	Outlet Concentration Benzoic Acid	Outlet Concentration Ethyl Benzoate
s	s	s	s	%	M	M
408	110	314	204	5.8	1.47	0.09
828	511	728	217	5.8	1.47	0.09
1248	910	1141	231	6.4	1.46	0.10
1667	1304	1552	248	7.1	1.45	0.10
2084	1693	1959	267	7.1	1.45	0.11
2504	2080	2368	288	7.7	1.44	0.12
2923	2460	2774	314	8.3	1.43	0.13
3342	2833	3177	344	9.0	1.42	0.14
3763	3198	3578	380	9.6	1.41	0.15
4182	3549	3972	422	10.9	1.39	0.17
4603	3885	4360	474	12.2	1.37	0.18
5024	4199	4736	537	13.5	1.35	0.20
5444	4481	5094	613	14.7	1.33	0.23
5864	4722	5422	700	16.7	1.30	0.25

Table S3. Time each sample was measured, left and entered the reactor and corresponding reaction time, along with conversion and outlet concentrations of benzoic acid and ethyl benzoate for the second MBDoE Ramp F experiment. The initial flowrate was 9.13 μL/min, the flowrate was ramped down at a rate of 0.043 μL/min^2, while the temperature was held constant at 139.4 °C and the feed concentration was 1.55 M.

$t_{M,i}$ Time the sample was measured	$t_{In,i}$ Time the sample entered the reactor	$t_{L,i}$ Time the sample left the reactor	τ_i Sample reaction time	X Conversion	Outlet Concentration Benzoic Acid	Outlet Concentration Ethyl Benzoate
s	s	S	s	%	M	M
152	NA	NA	623	44.9	0.86	0.70
571	NA	271	643	45.5	0.85	0.70
991	17	680	663	46.2	0.84	0.72
1411	404	1089	685	47.4	0.82	0.73
1830	787	1496	709	48.1	0.81	0.74
2251	1170	1904	734	48.7	0.80	0.76
2670	1549	2309	760	50.0	0.78	0.78
3090	1925	2714	789	51.3	0.76	0.79
3510	2298	3117	819	51.9	0.75	0.81
3931	2668	3520	852	53.8	0.72	0.83
4350	3033	3920	887	55.1	0.70	0.86
4770	3393	4318	925	56.4	0.68	0.87
5190	3749	4715	966	57.7	0.66	0.90
5610	4098	5109	1010	59.0	0.64	0.92

Table S4. Time each sample was measured, left and entered the reactor, corresponding reaction time, and the reactor temperature at the time the samples entered and left the reactor, along with conversion and outlet concentrations of benzoic acid and ethyl benzoate for the MBDoE Ramp FT experiment. The initial flowrate was 10.1 μL/min, the flowrate was ramped down at a rate of 0.05 μL/min^2, while the initial temperature was 139.2 °C, and it was ramped down at a rate of 0.537 °C/min. The feed concentration of benzoic acid was held constant at 1.56 M.

$t_{M,i}$ **Time the sample was measured**	$t_{In,i}$ **Time the sample entered the reactor**	$t_{L,i}$ **Time the sample left the reactor**	τ_i Sample reaction time	$T_{0,i}$ Reactor temperature at time $t_{In,i}$	$T_{L,i}$ Reactor temperature at time $t_{L,i}$	X Conversion	Outlet Conc. Benzoic Acid	Outlet Conc. Ethyl Benzoate
s	s	s	s	°C	°C	%	M	M
419	NA	NA	577	139.2	139.2	41.5	0.91	0.64
840	NA	150	596	139.2	134.2	39.6	0.94	0.62
1260	354	561	617	136.0	130.5	35.1	1.01	0.55
1679	739	971	639	132.6	126.9	31.2	1.07	0.49
2099	1124	1379	663	129.1	123.2	26.7	1.14	0.42
2519	1505	1786	688	125.7	119.6	23.5	1.19	0.37
2939	1883	2193	716	122.3	115.9	19.7	1.25	0.31
3359	2258	2599	745	119.0	112.3	17.1	1.29	0.27
3779	2629	3003	777	115.7	108.7	14.5	1.33	0.22
4199	2996	3406	811	112.4	105.1	12.6	1.36	0.19
4619	3358	3807	848	109.1	101.6	10.0	1.40	0.16
5038	3714	4206	888	106.0	98.0	8.7	1.42	0.13
5457	4064	4602	931	102.8	94.5	7.5	1.44	0.11
5876	4407	4995	979	99.8	91.0	6.2	1.46	0.09

1. C. Waldron, A. Pankajakshan, M. Quaglio, E. Cao, F. Galvanin and A. Gavriilidis, *Reac. Chem. Eng.*, 2019, **4**, 1623-1636.