Supporting Information

Flow markers in microreactors: a generally applicable method for analyzing flow rates during reactions

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Section 1 Derivation equation 1

The flow rate of a fluid in the microreactor system (Q_A) can be calculated from the flow marker concentration measured by chromatography. For the calculation, Equation 1 can be used.

$$Q_A = \frac{[M_A]V_{dil}}{t_{coll}\left([M_A]_0 - [M_A]\right)} \qquad \text{(Equation 1)}$$

$[M_A]$ is the actual concentration of the flow marker of fluid A in the sample vial, $[M_A]_0$ is the concentration of the flow marker in fluid A (before pumping into the chip), V_{dil} is the volume of diluting fluid in the vial, prior to sample collection and t_{coll} is the duration of sample collection.

The actual concentration $[M_A]$ can be calculated as a function of the starting concentration $[M_A]_0$:

$$[M_A] = \frac{[M_A]_0 V_{flow}}{V_{flow} + V_{coll}} \qquad \text{(Equation 2)}$$

In which V_{flow} is the volume of fluid A collected during t_{coll}.

V_{flow} can be defined as

$$[V_{flow}] = Q_A t_{coll} \qquad \text{(Equation 3)}$$

When Equation 3 is substituted into Equation 2, the flow as depicted by Equation 1 can be obtained.

Section 2 Channel design

In Figure S1, the mask design of the chip used for all experiments is depicted. Note that two reactors are present on the chip: one short reactor (single line) and one long reactor (with multiple lines and turns).

The upper reactor's main inlets are placed in left upper corner (no. 1 and 2). The inlet port for the base (DIPEA) is no. 3, the outlet no. 4.

The lower reactor's main inlets are numbered 5 and 6, the DIPEA inlet port is no. 8 and the outlet is no. 7.

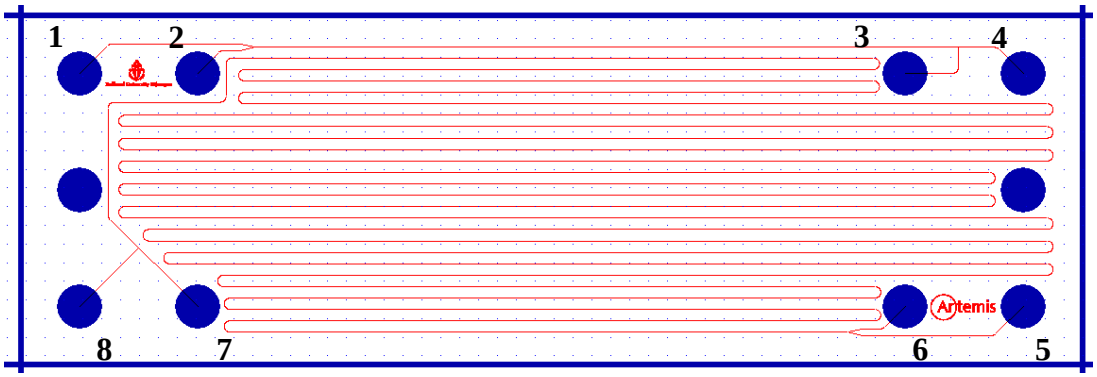

Figure S1: The channel design of the microreactor.

Section 3 Example of chromatographic data

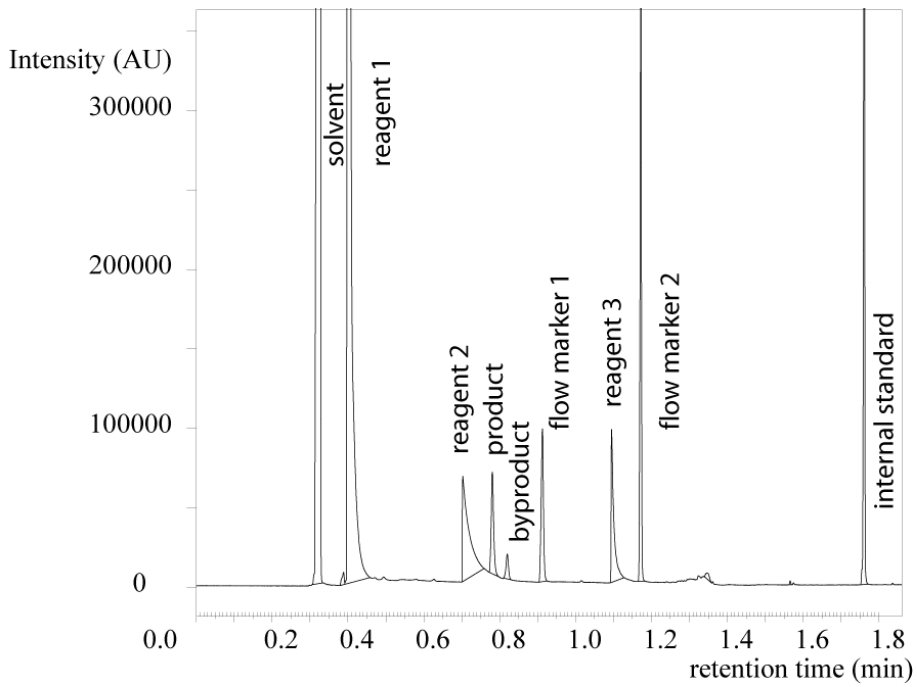

Figure S2: A gas chromatogram of a typical microreactor sample containing flow markers. The flow markers have been selected in such a way that they do not interfere with the quantification of the reaction components. The reagents, products, etc. are listed below.

Component name listed in figure	Compound
Solvent	Dichloromethane
Reagent 1	*N*,*N*-diisopropylethyl amine
Reagent 2	DMSO
Product	Benzaldehyde
Byproduct	Benzyl 2,2,2-trifluoroacetate
Flow marker 1	1,2-dichlorobenzene
Reagent 3	Benzyl alcohol
Flow marker 2	5-bromo-3,5-dimethylbenzene
Internal standard	1-bromonaphthalene

Section 4 Flow rate data

Table S3: Flow check experiment: set and flow rates calculated from GC data, accuracy and precision.

Q_A(set)	Q_B(set)	t_{coll}	Q_A(calculated)			Q_B(calculated)			ΔQ_A[1]	ΔQ_B[1]	σ_A[2]	σ_B[2]
µL/min	*µL/min*	*min*		*µL/min*			*µL/min*		*%*	*%*	*%*	*%*
66.67	33.33	0.75	61.94	62.64	62.94	29.27	31.05	30.94	-6.24	-8.74	0.82	3.27
36.43	18.21	1.37	33.73	35.44	34.84	16.34	17.38	17.14	-4.84	-6.91	2.51	3.22
19.91	9.95	2.51	18.24	19.42	18.83	9.04	9.69	9.17	-5.41	-6.59	3.13	3.68
10.88	5.44	4.60	9.84	10.28	10.58	4.85	5.08	5.24	-5.93	-7.03	3.66	3.88
5.94	2.97	8.41	5.53	5.78	5.76	2.73	2.86	2.86	-4.29	-5.21	2.41	2.59
3.25	1.62	15.39	3.05	3.07	3.22	1.53	1.50	1.57	-4.16	-5.50	2.90	2.23
52.22	47.78	0.96	48.37	50.32	49.90	43.22	46.07	44.79	-5.16	-6.46	2.07	3.20
28.54	26.11	1.75	26.89	28.30	18.95	24.75	25.33	18.54	-13.40	-12.40	20.40	16.45
8.52	7.80	5.87	8.10	8.11	8.15	7.31	7.41	7.50	-4.70	-4.97	0.33	1.29
4.66	4.26	10.74	4.22	4.62	4.50	3.91	4.17	4.08	-4.55	-4.88	4.56	3.21
2.54	2.33	19.65	2.34	2.41	2.40	2.17	2.20	2.20	-6.41	-5.88	1.71	0.80
37.39	62.61	0.80	30.32	38.36	36.49	65.52	49.30	63.70	-6.24	-4.96	12.00	14.93
20.43	34.21	1.46	20.13	19.27	19.01	30.02	32.93	31.45	-4.70	-8.03	3.02	4.63
11.17	18.70	2.67	9.77	10.30	10.67	16.81	17.01	18.94	-8.24	-5.95	4.43	6.69
3.33	5.58	8.96	3.06	3.09	3.24	5.35	4.77	5.46	-6.07	-6.98	3.17	7.18
1.82	3.05	16.39	1.56	1.59	2.07	2.45	2.89	3.46	-4.65	-3.81	16.48	17.40
24.60	75.40	0.66	22.00	24.21	23.88	72.01	74.88	75.29	-5.04	-1.77	5.09	2.42
13.45	41.20	1.21	11.11	12.40	13.44	37.42	38.96	39.90	-8.40	-5.92	9.47	3.24
2.19	6.72	7.44	2.01	2.00	2.18	6.46	6.54	6.78	-5.87	-1.94	4.96	2.49
1.20	3.67	13.61	1.07	1.09	1.10	3.58	3.50	3.33	-9.39	-5.54	1.09	3.66
15.13	84.87	0.59	14.12	13.38	14.53	82.21	82.93	81.18	-7.42	-3.25	4.14	1.07
8.27	46.37	1.08	7.95	6.11	8.50	48.00	45.33	45.10	-9.05	-0.49	16.60	3.49
4.52	25.34	1.97	3.99	3.64	4.32	23.62	22.54	24.19	-11.84	-7.46	8.49	3.59
2.47	13.85	3.61	2.18	1.97	2.79	11.23	10.71	19.61	-6.38	0.01	18.45	36.09
1.35	7.57	6.61	1.18	1.15	1.38	7.41	7.56	7.40	-8.33	-1.48	9.90	1.16
8.88	91.12	0.55	7.46	8.58	9.67	87.37	90.64	95.41	-3.48	0.02	12.88	4.44
4.85	49.79	1.00	4.45	4.11	4.74	48.82	47.86	48.56	-8.64	-2.77	7.09	1.03
2.65	27.21	1.84	2.23	2.33	1.84	24.82	27.24	19.90	-19.56	-11.84	11.97	15.59
1.45	14.87	3.36	1.03	1.08	1.87	13.66	10.80	15.91	-8.51	-9.49	35.34	19.04
0.43	4.44	11.26	0.30	0.47	0.30	3.29	3.18	2.70	-17.57	-31.17	28.10	10.12

[1] Difference between the average over triplicates and the set flow rate. [2] standard deviations of triplicates relative over average calculated flow rates.

Table S4. Swern-Moffatt oxidation: set and flow rates calculated from GC data, accuracy and precision.

Q_A(set)	Q_B(set)	t_{coll}	Q_A(calc)			Q_B(calc)			ΔQ_A [1]	ΔQ_B [1]	σ_A [2]	σ_B [2]
µL/min	*µL/min*	*min*		*µL/min*			*µL/min*		*%*	*%*	*%*	*%*
16.20	37.27	3.09	9.81	11.78	12.15	33.52	39.35	40.16	-30.61	1.08	11.19	9.62
28.03	89.71	1.78	20.76	21.87	21.32	101.40	102.64	102.16	-23.95	13.77	2.60	0.61
35.68	82.07	1.40	27.91	23.22	24.36	92.45	92.74	94.39	-29.48	13.56	9.72	1.12
112.6	146.4	0.44	99.84	107.65	107.56	165.17	177.23	176.99	-6.77	18.22	4.27	3.98
65.41	52.33	0.76	57.66	59.81	61.42	54.83	56.67	57.22	-8.85	7.47	3.17	2.22
12.73	40.74	3.93	10.44	10.38	10.11	46.73	46.33	47.13	-19.04	14.70	1.66	0.86
14.07	39.40	3.55	12.37	12.42	12.68	44.91	45.20	45.63	-11.26	14.83	1.31	0.80
92.53	166.6	0.54	83.16	82.28	77.51	199.55	198.28	190.81	-12.48	17.80	3.76	2.41
143.9	115.2	0.35	139.39	127.79	138.52	132.34	120.73	132.39	-6.05	11.58	4.78	5.23
23.25	30.23	2.15	21.42	21.32	21.56	33.30	33.83	34.31	-7.81	11.87	0.55	1.50
29.71	23.77	1.68	26.79	27.12	26.69	25.33	25.57	25.45	-9.57	7.07	0.84	0.48
61.69	197.4	0.81	49.91	51.14	51.28	225.22	228.21	231.05	-17.69	15.58	1.48	1.28
42.05	75.69	1.19	37.70	38.16	37.73	86.28	87.30	87.63	-9.97	15.02	0.68	0.81
19.10	34.38	2.62	17.15	17.48	17.83	39.87	39.50	39.87	-8.44	15.61	1.95	0.54
68.18	190.9	0.73	59.70	63.10	53.21	214.05	222.27	183.65	-13.95	8.25	8.57	9.84
30.99	86.76	1.61	27.06	28.22	27.66	99.94	101.24	99.33	-10.77	15.46	2.10	0.97
78.51	180.6	0.64	72.48	71.92	71.78	216.98	216.21	214.95	-8.22	19.64	0.52	0.47
51.19	66.55	0.98	45.53	45.27	44.92	76.58	77.30	77.41	-11.63	15.85	0.68	0.58
3.95	7.11	5.06	3.50	3.47	3.51	7.99	8.03	8.23	-11.51	13.70	0.61	1.57
7.37	16.95	2.71	6.73	6.49	6.50	20.02	19.49	19.75	-10.85	16.49	2.05	1.34
6.14	4.91	3.26	5.26	5.32	5.43	5.14	5.47	5.49	-13.17	9.17	1.63	3.61
10.58	13.75	1.89	9.13	8.78	9.49	15.39	15.07	15.71	-13.64	11.95	3.91	2.08
6.40	17.92	3.12	5.48	5.60	5.51	21.09	21.08	21.40	-13.62	18.22	1.07	0.87
13.51	10.81	1.48	11.53	12.15	11.90	11.41	12.57	12.13	-12.23	11.34	2.64	4.88
5.79	18.53	3.45	4.72	4.58	4.49	21.58	21.55	21.58	-20.64	16.38	2.49	0.07
4.81	6.25	4.16	4.47	4.27	4.25	7.05	6.86	7.16	-9.93	12.35	2.77	2.11
2.63	8.43	7.60	2.36	2.32	2.44	9.82	9.56	9.88	-9.83	15.76	2.57	1.76
2.91	8.15	6.87	2.68	2.64	2.62	9.47	9.30	9.36	-9.15	15.07	1.09	0.90
8.69	15.64	2.30	7.82	7.97	7.73	17.65	18.03	17.86	-9.78	14.12	1.52	1.05
3.35	7.71	5.97	2.94	2.89	2.95	8.78	8.74	8.94	-12.72	14.47	1.09	1.19
4.22	13.51	4.74	3.88	3.83	3.84	15.88	15.66	15.85	-8.82	16.95	0.69	0.74
21.67	17.33	0.92	19.36	20.84	20.97	18.76	19.71	19.67	-5.89	11.80	4.40	2.77
11.82	27.18	1.69	10.82	11.26	11.13	31.54	32.73	32.26	-6.34	18.37	2.04	1.86
5.37	12.36	3.72	4.97	4.97	4.97	14.52	14.50	14.58	-7.46	17.62	0.09	0.29
7.71	10.02	2.59	7.36	7.30	7.22	11.48	11.68	11.80	-5.41	16.31	0.91	1.37
9.85	7.88	2.03	8.73	9.62	9.69	8.57	9.06	9.14	-5.08	13.27	5.71	3.51
10.26	28.74	1.95	9.17	9.47	9.76	33.57	33.65	34.57	-7.76	18.08	3.10	1.64
6.33	11.40	3.16	5.83	6.12	5.83	12.94	13.75	13.34	-6.39	17.09	2.87	3.05
16.96	22.04	1.18	16.03	16.08	15.67	25.50	25.87	25.80	-6.06	16.69	1.40	0.77
9.29	29.71	2.15	8.70	8.71	8.64	35.35	35.43	35.39	-6.51	19.10	0.46	0.12
4.67	13.06	4.29	4.27	4.30	2.09	15.15	15.36	7.69	-23.80	-2.51	35.64	34.34
13.93	25.07	1.44	12.30	13.22	13.06	23.81	30.76	30.03	-7.67	12.48	3.82	13.54

[1] Difference between the average over triplicates and the set flow rate. [2] standard deviations of triplicates relative over average calculated flow rates.

Section 5 Flow rate deviation charts

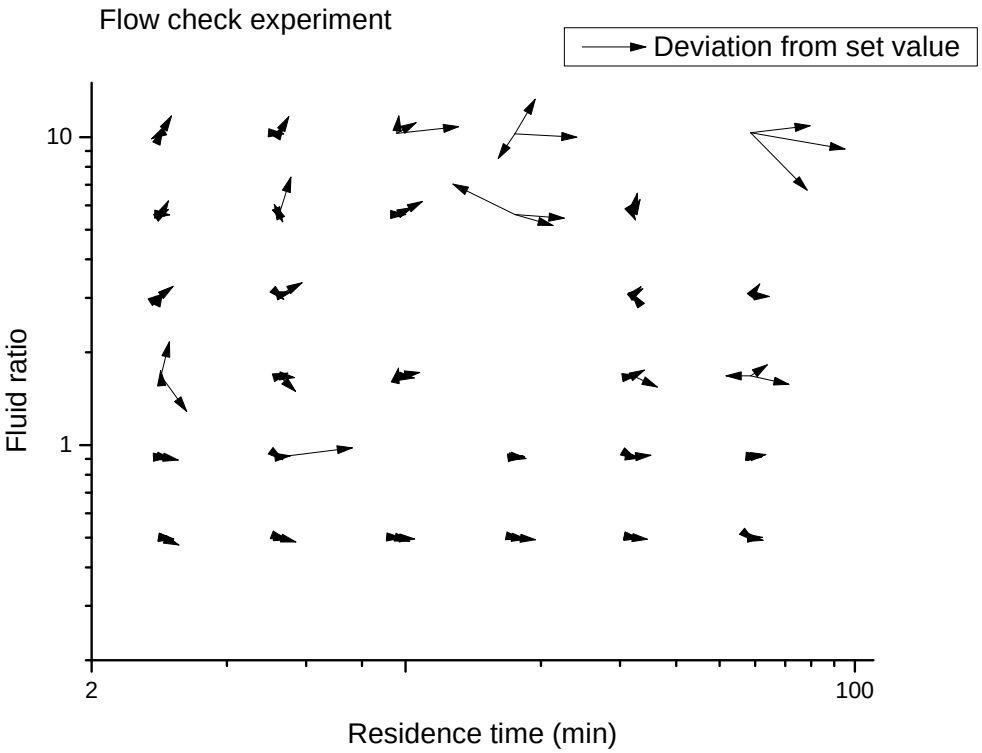

Figure S5. Flow deviations in a test experiment. Deviations are shown as vectors in an x/y-matrix in which x-values represent the residence time in the chip, and y-values represent the ratio between fluid B and A. The arrows' starting points represent the theoretical, or set, value, the endpoints represent the values calculated from GC responses.

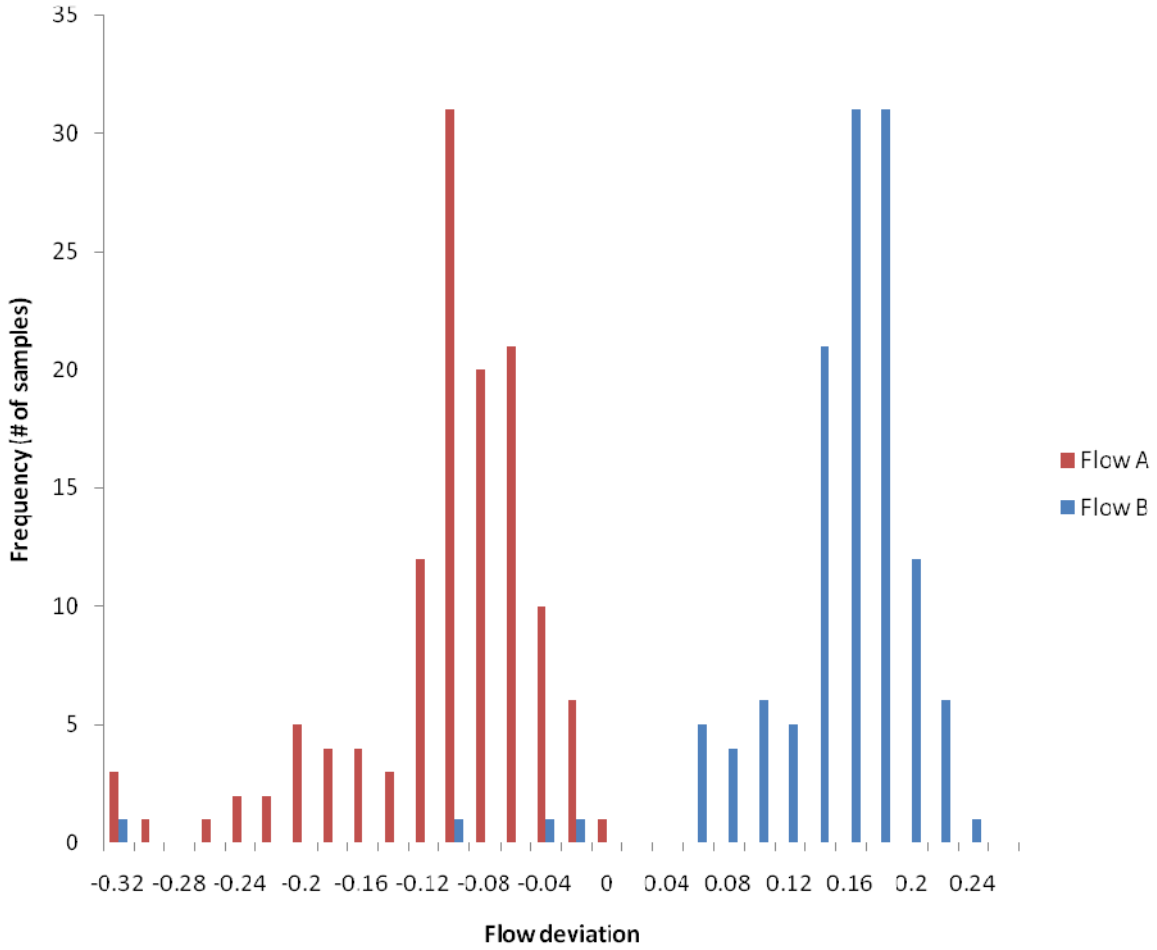

Figure S6. A histogram of flow deviations in % of the Swern Moffatt oxidation model reaction.