

Electronic Supplementary Information

Accelerating Reaction Modeling Using Dynamic Flow Experiments, Part 2: Development of a Digital Twin

Klara Silber,^{a,b} Peter Sagmeister,^{a,b} Christine Schiller,^{a,b} Jason D. Williams,^{a,b}
Christopher A. Hone,^{*a,b} and C. Oliver Kappe^{*a,b}

^aCenter for Continuous Flow Synthesis and Processing (CC FLOW), Research Center
Pharmaceutical Engineering GmbH (RCPE), Inffeldgasse 13, Graz, Austria

^bInstitute of Chemistry, University of Graz, Heinrichstrasse 28, 8010 Graz, Austria.

Email: christopher.hone@rcpe.at, oliver.kappe@uni-graz.at

Table of Contents

1	General Information.....	3
2	Experimental conditions and configuration	3
3	Residence time distribution (RTD) analysis	3
4	Flowsheet modeling	6
5	Kinetic fitting	7
6	Model Validation	10
8	Disturbances.....	15
8	References.....	16

1 General Information

2 Experimental conditions and configuration

Full details regarding the experimental conditions, flow configuration and analysis are reported in part 1 of this contribution.¹

3 Residence time distribution (RTD) analysis

The data points collected by the NMR and FT-IR analysis were obtained as concentration values. The equations used to characterize the reactor and the system were described by Levenspiel.² The analysis assumed that the injected plug was a perfect pulse at the inlet, because the concentration was not measured before the reactor.

The concentration data points over time were numerically integrated to obtain the area under the curve:

$$A = \sum C_i \cdot \Delta t \quad (1)$$

Where A is the area inside the curve, C_i is the concentration in one point, Δt is the difference of time between two points.

Subsequently, the concentration of each measurement was divided by the area to obtain the exit-age distributed function:

$$E(t) = \frac{C_i}{A} \quad (2)$$

Where $E(t)$ is the exit-age distribution depending on time, \bar{t} is the mean residence time, θ is the dimensionless normalized time and E_θ is the exit-age distribution depending on θ . The dimensionless normalized time, θ , was calculated by dividing time by the mean residence time:

$$\theta = \frac{t_i}{\bar{t}} \quad (3)$$

Where t_i is time at a particular instant in time.

And:

$$\bar{t} = \frac{\sum t_i \cdot C_i \cdot \Delta t}{\sum C_i \cdot \Delta t} \quad (4)$$

Where \bar{t} is the mean is residence time.

$E(\Theta)$ was obtained by multiplying $E(t)$ by the mean residence time:

$$E_{\theta} = E(t) \cdot \bar{t} \quad (5)$$

The variance, σ^2 , represents the spread of the distribution as it passes the vessel exit and has units of time:

$$\sigma^2 = \frac{\sum t_i^2 \cdot C_i \cdot \Delta t}{\sum C_i \cdot \Delta t} - \bar{t}^2 \quad (6)$$

Therefore the normalized variance is calculated using the following equation:

$$\sigma_{\theta}^2 = \frac{\sigma^2}{\bar{t}^2} \quad (7)$$

The axial dispersion coefficient divided by the longitude and the flow speed is the vessel dispersion number:

$$\left(\frac{D}{u \cdot L} \right) = \frac{\sigma_{\theta}^2}{2} \quad (8)$$

Where the parameter D , called the longitudinal or axial dispersion coefficient, characterizes the degree of back mixing during flow. L is the system longitude and u is the flow speed. If the vessel dispersion number tends to zero, then there is negligible dispersion, hence it is plug flow. On the other hand, if the dispersion number tends to infinite, then there is large dispersion, hence mixed flow.

The Bodenstein (Bo) number was also calculated using the experimental data. The Bodenstein number is calculated by multiplying the mean residence time by two and dividing it by the variance:

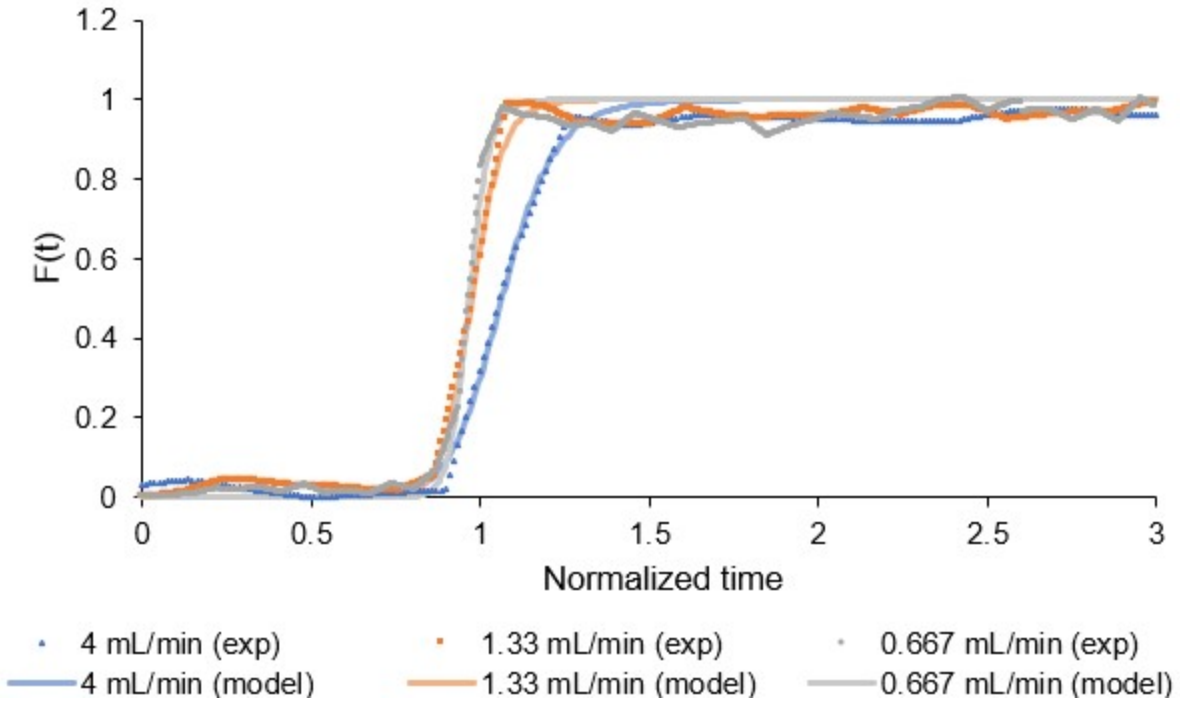
$$Bo = \frac{2 \cdot \bar{t}}{\sigma^2} \quad (9)$$

A Bodenstein number higher than 100 indicates plug flow behavior. A value below 100 indicates there is some axial dispersion presence and indicates more CSTR-like behavior.

The axial dispersion (D_{ax}) number can then be calculated:

$$D_{ax} = \frac{u \cdot L}{Bo} \quad (10)$$

Where u represents the flow velocity and L is the length of the reactor.



	Flow rate (mL/min)		
	4.00 mL/min	1.33 mL/min	0.67 mL/min
Bo (-)	121	335	600
D_{ax} (m ² /s)	0.00183	0.000219	6.13E-05

Figure S1. Assessment of residence time distribution within the reactor system using inline FTIR. Reactor temperature at 100 °C. Model corresponds to sigmoidal fitting of the data points at each flow rate.

Overall, the calculated values from the FTIR analysis show that the system can be considered as plug flow with a flat velocity profile. Thus, the influence of dispersion on the measured rate parameters will be very small.

4 Flowsheet modeling

A flowsheet was created, see Scheme 2 in the main manuscript, and the experimental conditions were inputted. The stoichiometry was defined based on Scheme 1 within the manuscript. The reaction was simulated using dynamic conditions.

Mode of operation: Dynamic

Equipment and operation

Equipment specification

- Length: 2.60 m
- Specify area or diameter: Area
- Cross-sectional area: 0.785 mm²
- Inaccessible volume fraction: 0 m³/m³

Material flow

- Axial dispersion specification: Fixed
- Axial dispersion coefficient: 0.0051 m²/s
- Number of tubes: 1

OK Cancel Reset all Help

Figure S2. Equipment and operation input values for the digital twin.

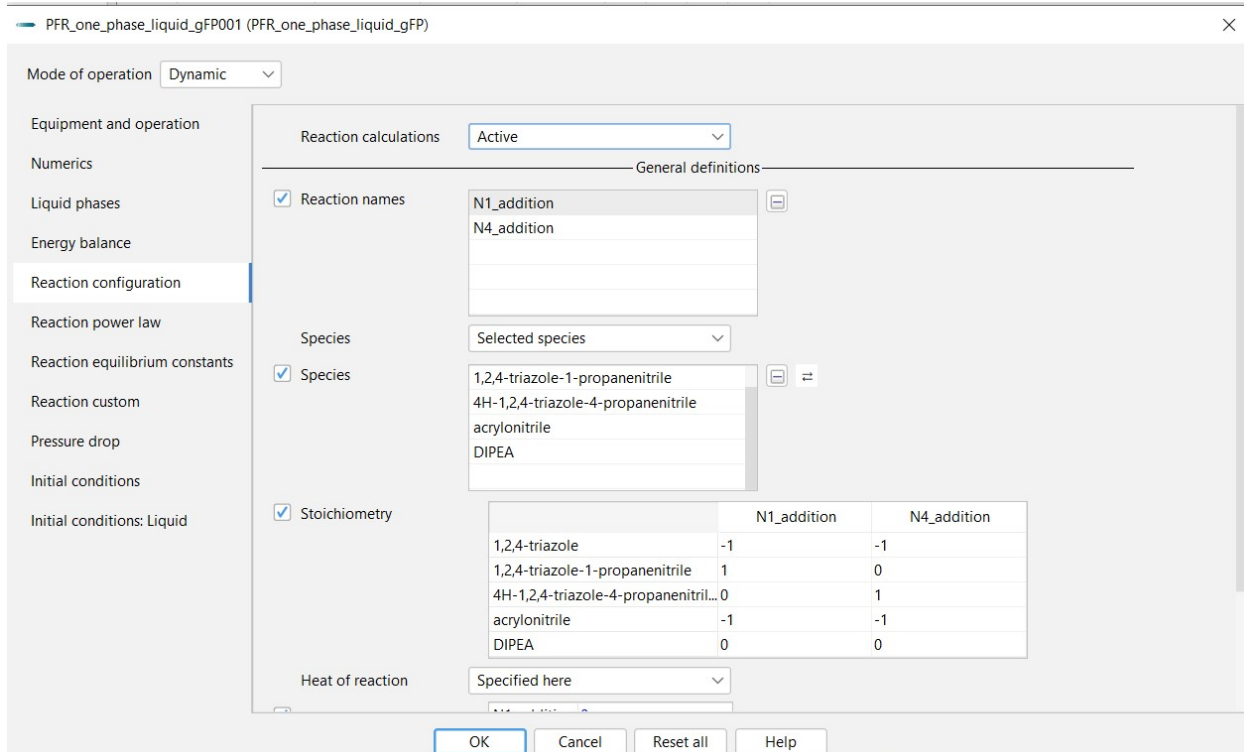


Figure S3. Reaction configuration inputted for the final model fit.

5 Kinetic fitting

The kinetic fitting was achieved by using a modified form of the Arrhenius expression for parameter estimation and optimization with a reference temperature:

$$k = \exp \left[\log (A_{T_0}) - \frac{Ea}{R} \left(\frac{1}{T} - \frac{1}{T_0} \right) \right] \quad (11)$$

A linear variance model was applied since it is appropriate for datasets that include small values as is the case for the isomer product. A linear variance model was applied for the fitting:

$$\sigma = |\alpha Z + \beta| \quad (12)$$

σ is the standard deviation applied, α is a constant relative term applied (a value of 1 corresponds to 100% of the measured value), β is a constant term and z is the model prediction of the measured quantity. In this study: $\alpha = 0.02$ and $\beta = 0.001$ mol/L.

The confidence limit was based on the assumption of a normal distribution for the errors, with 95% corresponding to 1.96 times the standard error of the parameter fit.

The maximum likelihood goal was captured through the following objective function:

$$\Phi = \frac{N}{2} \ln(2\pi) + \frac{1}{2} \min_{\theta} \left\{ \sum_{i=1}^{NE} \sum_{j=1}^{NV_i} \sum_{k=1}^{NM_{ij}} \left[\ln(\sigma_{ijk}^2) + \frac{(\tilde{z}_{ijk} - z_{ijk})^2}{\sigma_{ijk}^2} \right] \right\} \quad (13)$$

Where N is the total number of measurements, θ is the set of model parameters to be estimated, NE is the number of experiments performed, NV_i is the number of variables measured in the i^{th} experiment, NM_{ij} is the number of measurements of the j^{th} variable in the i^{th} experiment, σ_{ijk}^2 is the variance of the k^{th} measurement of variable j in experiment i , \tilde{z}_{ijk} is the k^{th} measured value of variable j in experiment i , and z_{ijk} is the k^{th} model-predicted value of variable j in experiment i .

Table S1 Correlation matrix for the fitted parameters given in Table 1 in the main manuscript.

		1	2	3	4
E _A (product formation)	1	1.0000	0.3338	0.0702	0.1785
E _A (isomer formation)	2	0.3338	1.0000	0.1835	-0.2245
log A (product formation)	3	0.0702	0.1835	1.0000	0.2938
log A (isomer formation)	4	0.1785	-0.2245	0.2938	1.0000

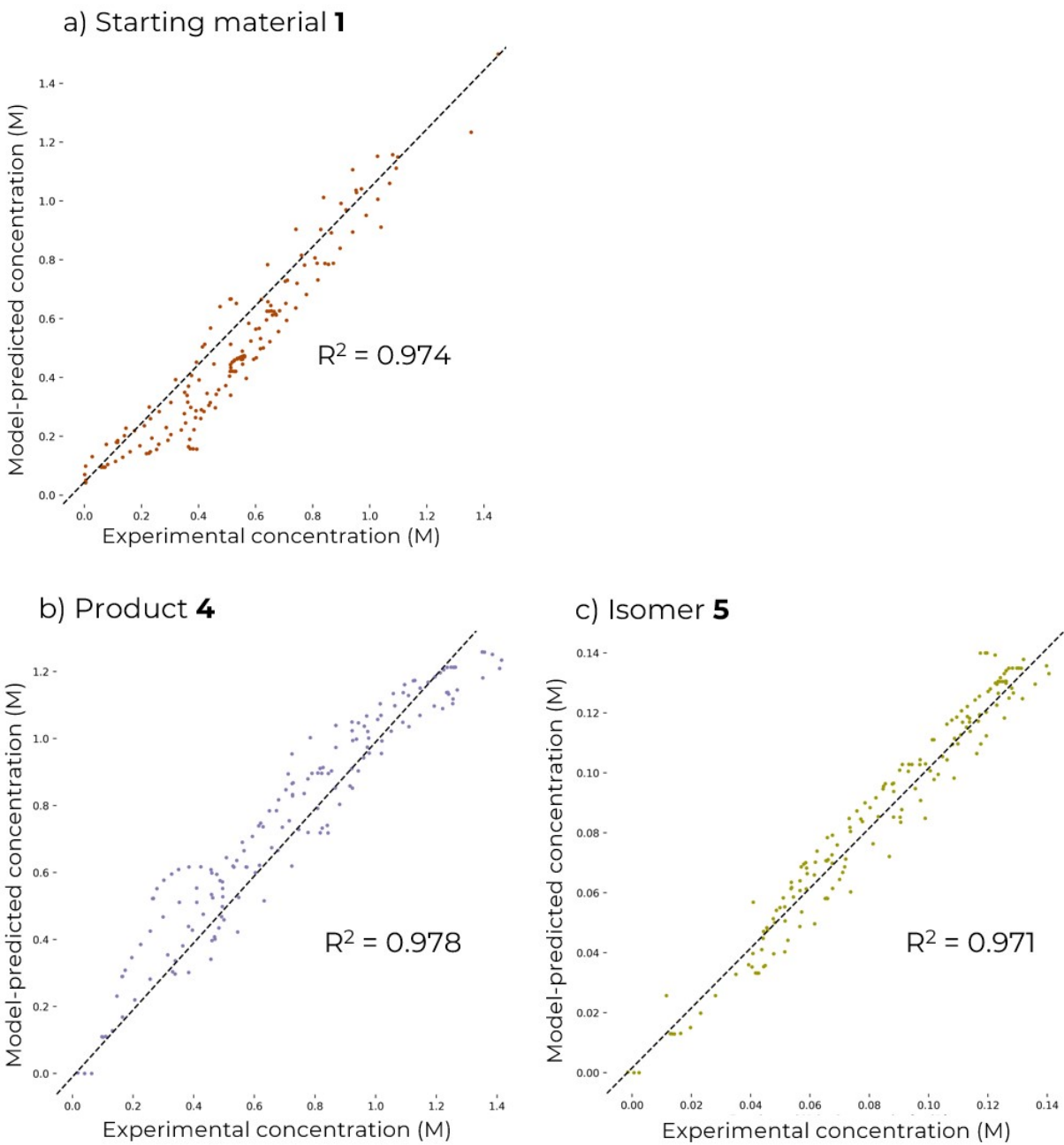


Figure S4. Parity plots for the reaction components **1**, **4** and **5**. Plot shows every 10th data point. Average $R^2 = 0.974$.

Table S2. Kinetic parameter estimates and standard errors (SE) based on 95% confidence level when the acrylonitrile (**3**) concentration values were included for the fitting. Logarithmic form of the pre-exponential factors, $\log(A_{T_0})$, are given at $T_0 = 120$ °C.

	$\log(A_{T_0}) \pm \text{SE}$ ($\text{mol}^{-1} \cdot \text{m}^3 \cdot \text{s}^{-1}$)	$E_a \pm \text{SE}$ ($\text{kJ} \cdot \text{mol}^{-1}$)
N1 Addition	-9.26 ± 0.001	68.5 ± 0.1
N4 Addition	-11.4 ± 0.002	67.1 ± 0.2

6 Model Validation

Table S3. Summary of flow ramp condition ranges. Experiment 3 was used for the fitting of the kinetic models. Experiments 2,4 and 5 were used for the model validation.

	t_{res} [s]	T [°C]	1 conc. [M]	3 eq	2 eq
3a	120	120	1.5	ramp: 2-0.8	0.1
3b	80	120	ramp: 0.75-1.5	1.5	0.1
3c	70	140	1.5	2	ramp: 0-0.1
3d	120	ramp: 140-100-140-100	1.5	ramp: 2-0.8-2	0.1
3e	80	ramp: 140-100-140-100	ramp: 0.75-1.5-0.75	1.5	0.1
2a	60	ramp: 140-100-140-100	1.5	2	0.1
2b	52	ramp: 140-100-140-100	0.65	2	0.2
2c	60	ramp: 140-100-140-100	1	1.1	0.075
4	ramp: 180-30-180-30	120	1.5	ramp: 2-0.8-2	0.1
5	ramp: 180-30-180-30	ramp: 120-140-100-120	1.5	ramp: 2-0.8-2	0.1

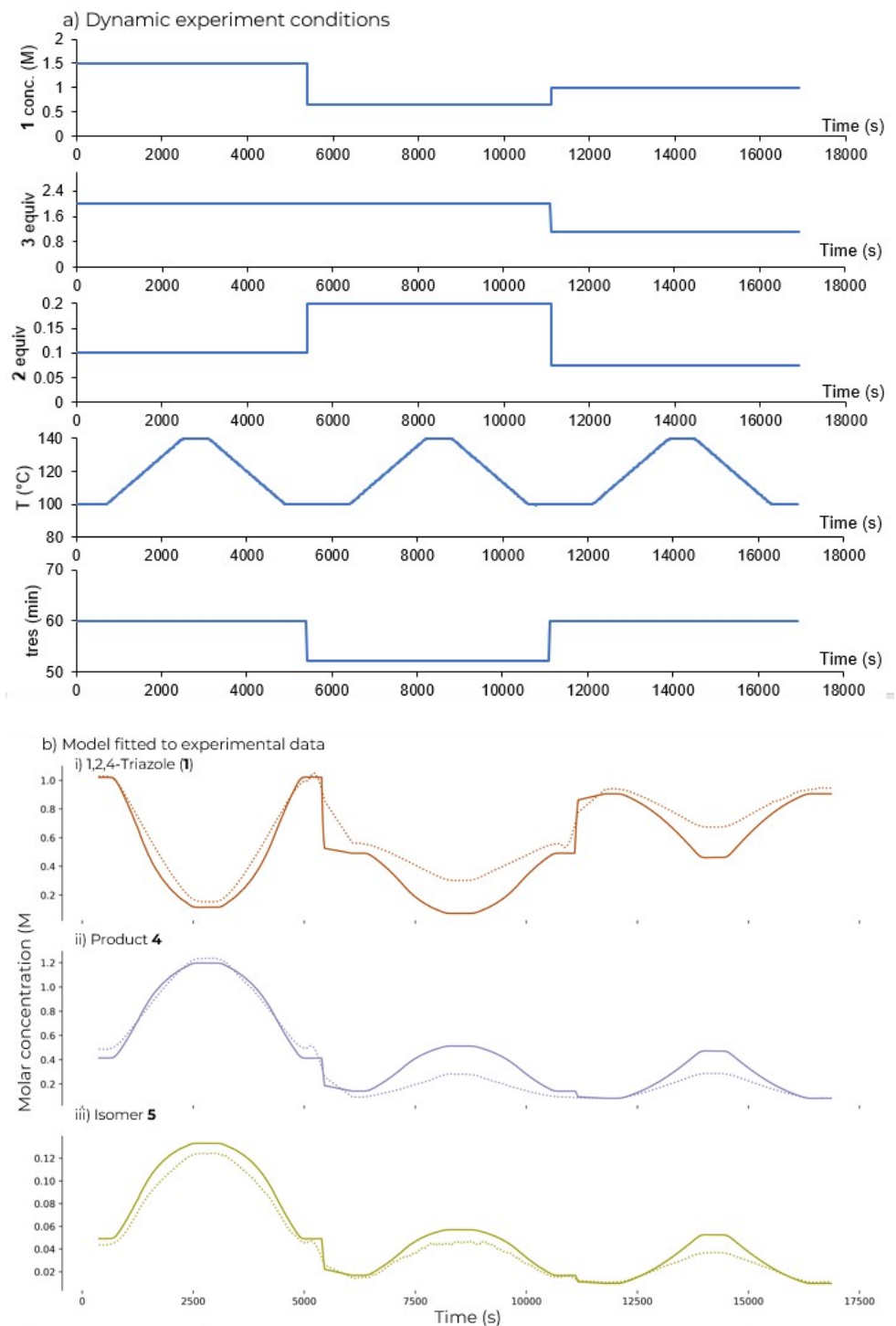


Figure S5. a) Conditions explored in a flow ramp used for model validation; b) Model trajectory and measured data for dynamic experiment using parameter values obtained in Table 1. Lines show fitted concentration; points show experimental data.

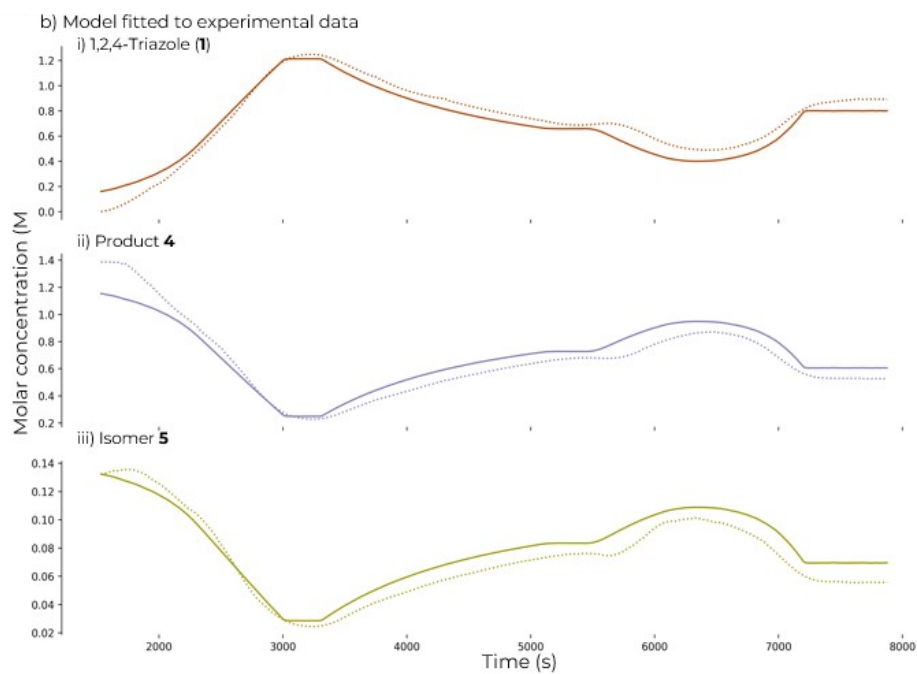
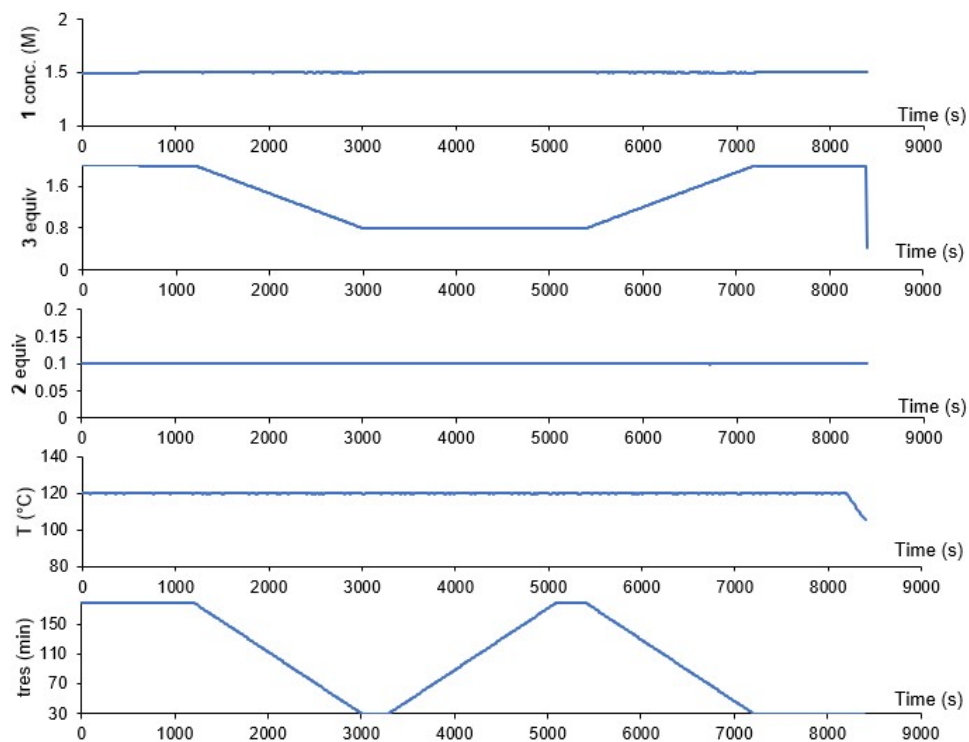


Figure S6. a) Conditions explored in a flow ramp used for model validation; b) Model trajectory and measured data for dynamic experiment using parameter values obtained in Table 1. Lines show fitted concentration; points show experimental data.

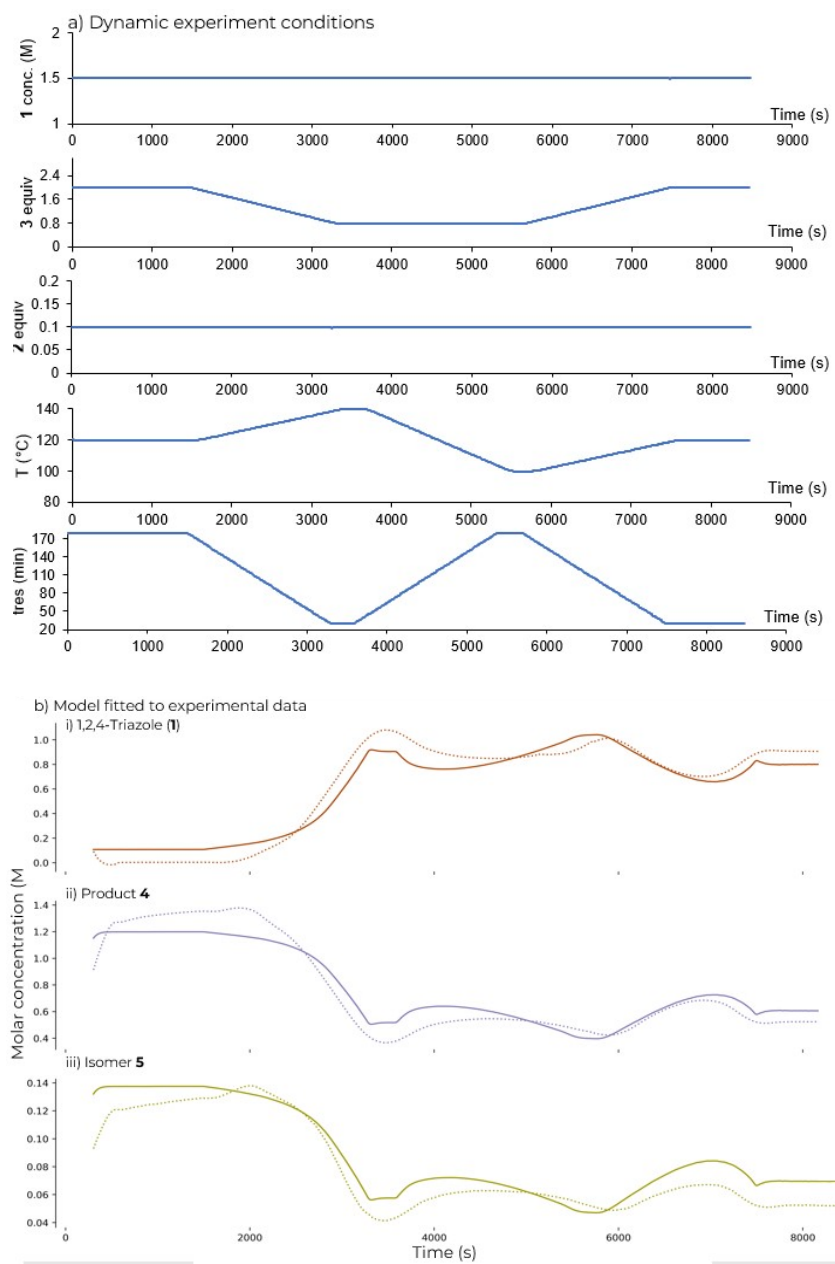


Figure S7. a) Conditions explored in a flow ramp used for model validation; b) Model trajectory and measured data for dynamic experiment using parameter values obtained in Table 1. Lines show fitted concentration; points show experimental data.

7 Self-optimization

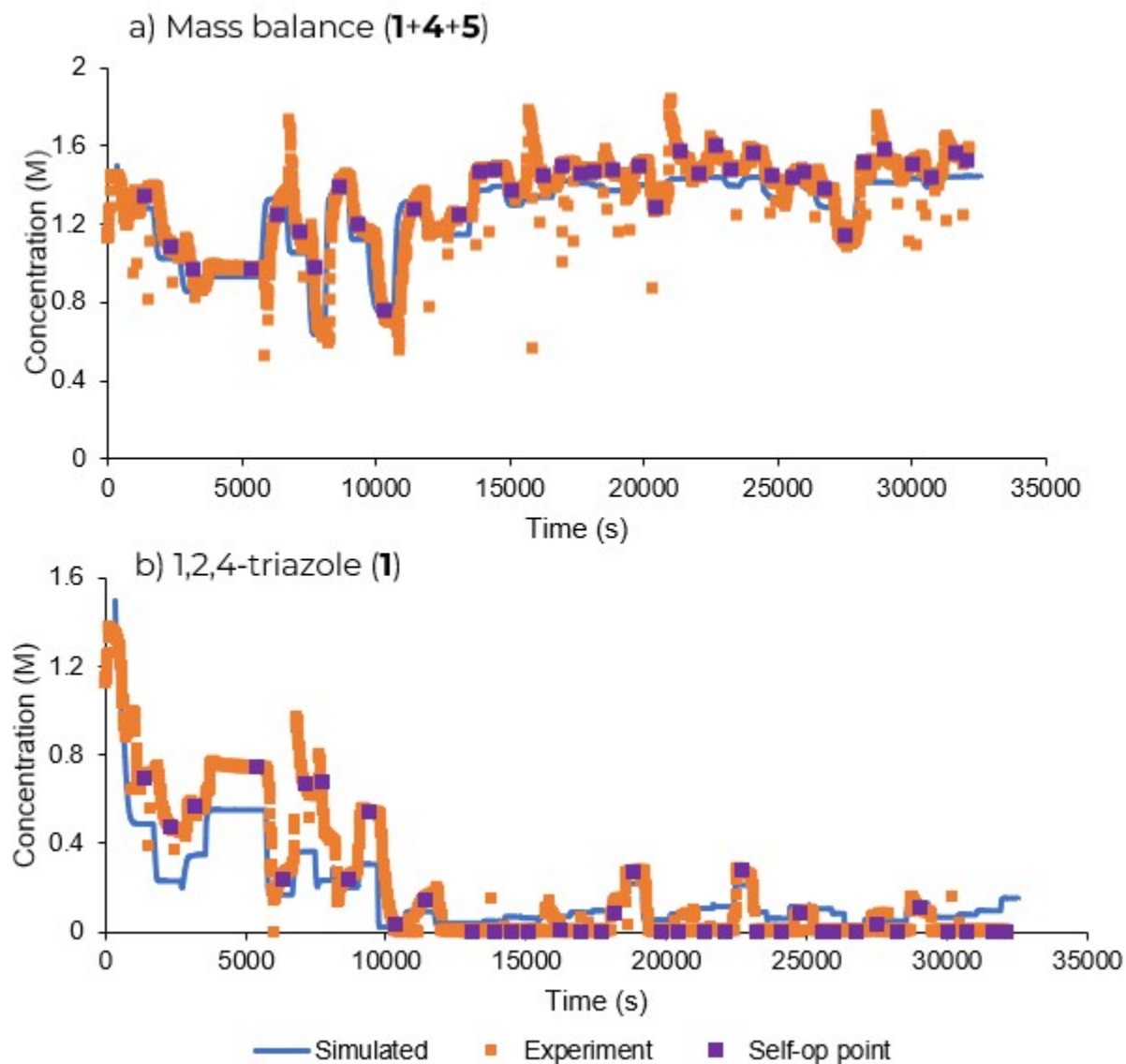


Figure S8. Model trajectory and measured data for the self-optimization using parameter values obtained in Table 1. Lines show fitted concentration; points show experimental data.

8 Disturbances

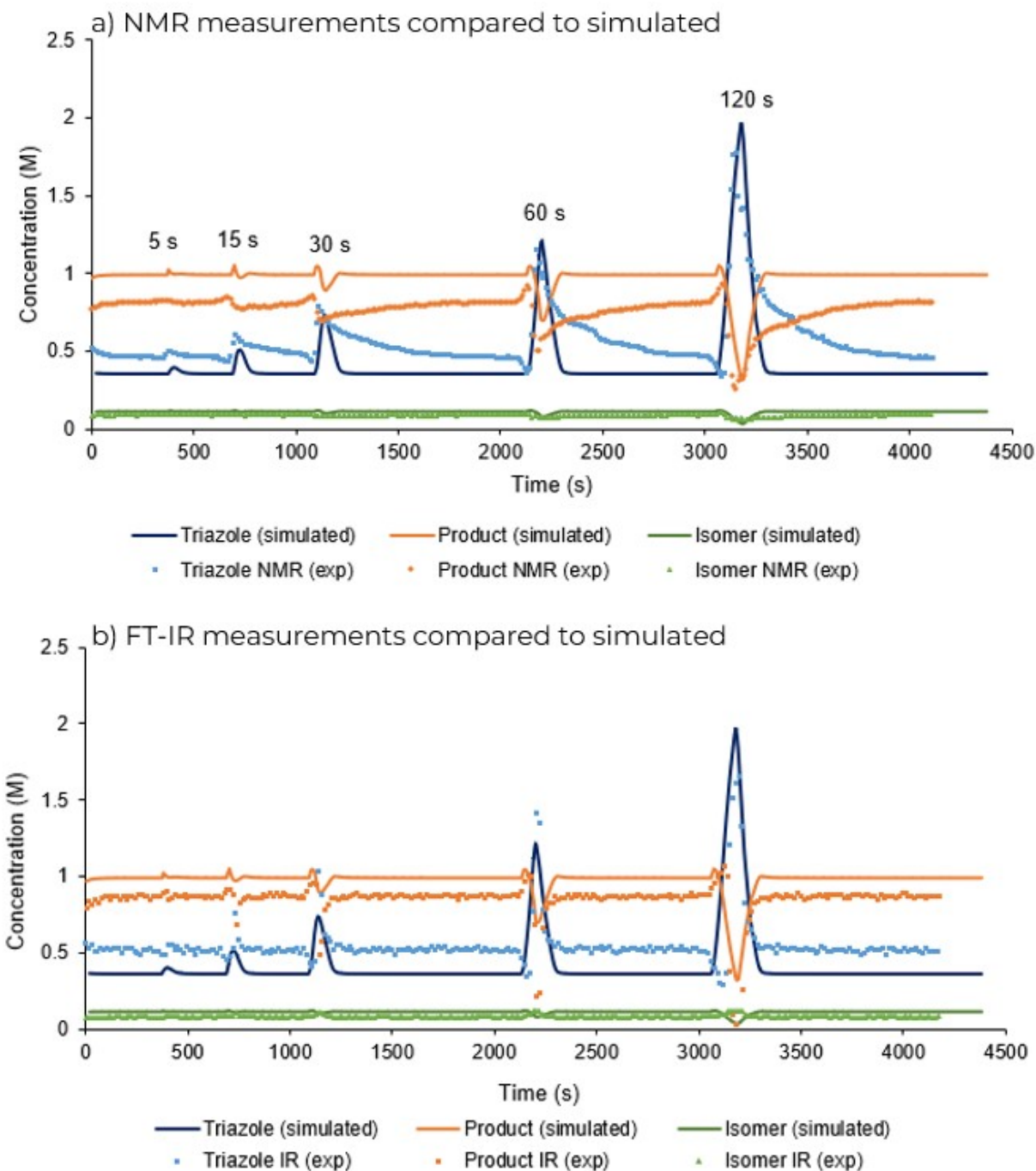


Figure S9. Simulated trajectories and experimental data for disturbance tests using parameter values obtained in Table 1 in the manuscript: i) compared to online NMR data; ii) compared to inline FTIR data. Lines show simulated concentration; points show experimental data. The times given on the figure refer to the length of time for which the acrylonitrile pump was switched off.

8 References

- 1 For more detail see part 1 of this contribution, entitled "Accelerating Reaction Modeling Using Dynamic Flow Experiments, Part 1: Design Space Exploration", P. Sagmeister, C. Schiller, P. Weiss, K. Silber, S. Knoll, C. A. Hone, J. D. Williams and C. O. Kappe, *React. Chem. Eng.*, 2023, DOI: 10.1039/D3RE00243H.
- 2 O. Levenspiel, *Chemical Reaction Engineering*, 3rd ed., John Wiley & Sons, Inc., New York, 1964. doi:10.1016/0009-2509(64)85017-X.