Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Automated Multi-objective Reaction Optimisation: Which Algorithm Should I Use?

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Contents

1 Multi-Objective Reaction Simulator – Test Problems

1.1 VdV1

(i)

$A_1 = 2.1 \times 10^{10}$ min^{-1}, $A_2 = 2.1 \times 10^{10}$ min^{-1}, $A_3 = 1.5 \times 10^{8}$ min^{-1},
$E_{a,1} = 81.1$ kJ mol^{-1}, $E_{a,2} = 81.1$ kJ mol^{-1}, $E_{a,3} = 71.2$ kJ mol^{-1}

$$minimise[-\ln(\%\,\boldsymbol{B}), \ln(STY)] \quad (1)$$

subject to:

Residence time/min ∈ [0.5, 10]
Temperature/°C ∈ [25, 100]
[**A**]/M = 1

(i)

(ii)

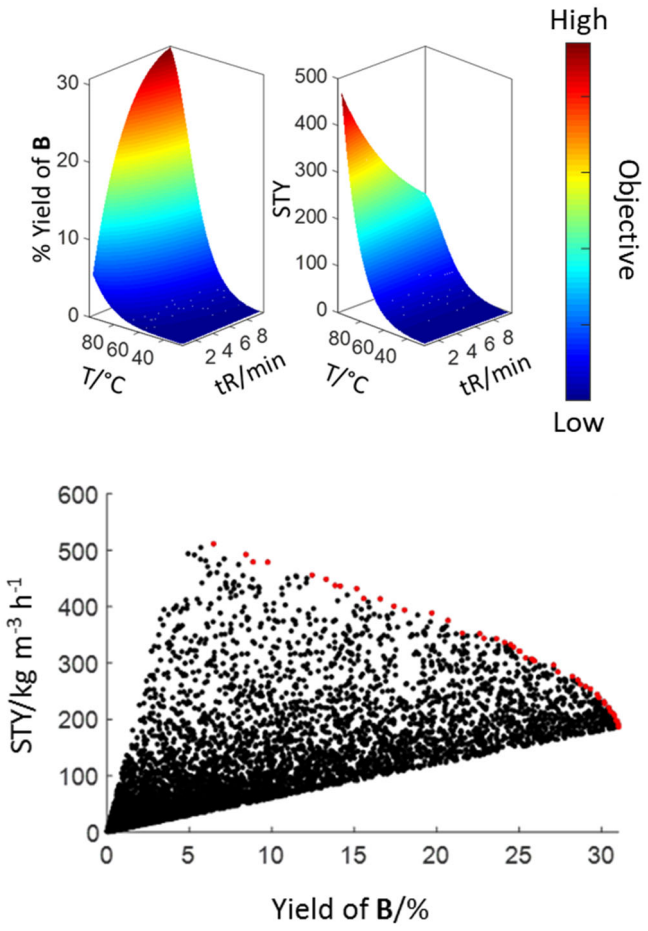


Figure S1. Graphical representations of the VdV1 test problem: (i) variable space; (ii) objective space. Black dots = possible solutions, red dots = non-dominated solutions.

1.2 SnAr1

(ii)

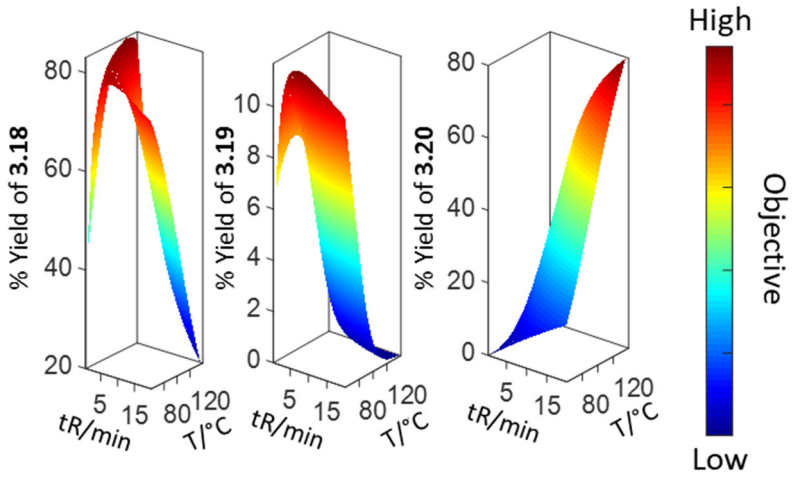
A_1 = 1.6 × 10^6 M^{-1} min^{-1}, A_2 = 1.4 × 10^4 M^{-1} min^{-1}, A_3 = 1.0 × 10^4 M^{-1} min^{-1},
A_4 = 3.7 × 10^8 M^{-1} min^{-1}, $E_{a,1}$ = 43.2 kJ mol^{-1}, $E_{a,2}$ = 35.3 kJ mol^{-1},
$E_{a,3}$ = 40.8 kJ mol^{-1}, $E_{a,4}$ = 68.9 kJ mol^{-1}

$$minimise[-\ln(\%\ \mathbf{3.18}), \ln(\%\ \mathbf{3.19}), \ln(\%\ \mathbf{3.20})] \quad (2)$$

subject to:

Residence time/min ∈ [0.5, 20]
Temperature/°C ∈ [60, 140]
[**3.16**]/M = 1
[**3.17**]/M = 3

(i)



(ii)

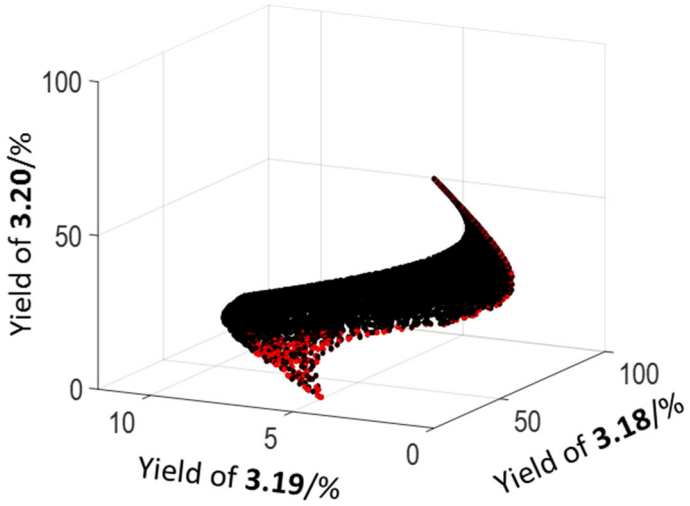


Figure S2. Graphical representations of the S_NAr1 test problem: (i) variable space; (ii) objective space. Black dots = possible solutions, red dots = non-dominated solutions.

1.3 SnAr2

$$minimise[\ln(\%\ \mathbf{3.19}), -\ln(RME), -\ln(STY)] \quad (3)$$

subject to:

Residence time/min ∈ [0.5, 2]

Temperature/°C ∈ [60, 140]

[**3.16**]/M ∈ [0.1, 2.0]

[**3.17**]/M ∈ [2, 5]

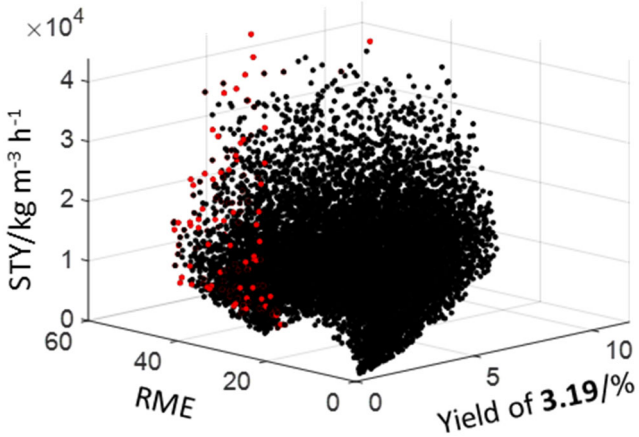


Figure S3. Graphical representations of the objective space for the S_NAr2 test problem. Black dots = possible solutions, red dots = non-dominated solutions.

1.4 Lactose1

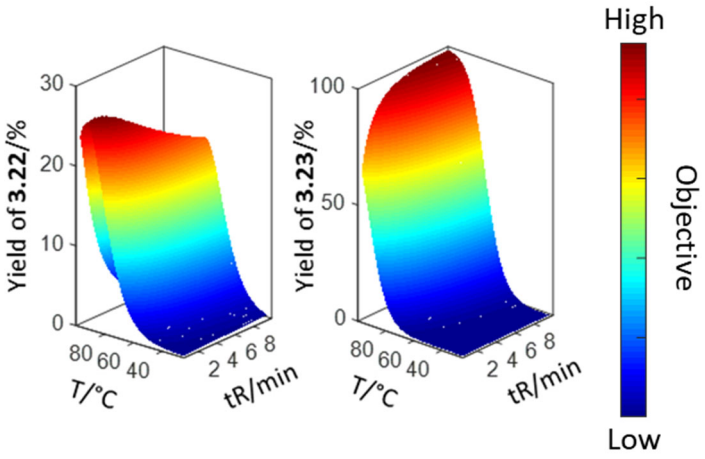
(iii)

pH = 11, A_1 = 9.5 × 10^{14} min^{-1}, A_2 = 7.0 × 10^{24} min^{-1}, A_3 = 4.0 × 10^{7} min^{-1},
$E_{a,1}$ = 105.1 kJ mol^{-1}, $E_{a,2}$ = 174.0 kJ mol^{-1}, $E_{a,3}$ = 54.9 kJ mol^{-1}

$$minimise[-\ln(\%\ \mathbf{3.22}), \ln(\%\ \mathbf{3.23})] \quad (4)$$

subject to: Residence time/min ∈ [0.5, 10]
Temperature/°C ∈ [25, 100]
[**3.21**]/M = 1

(i)



(ii)

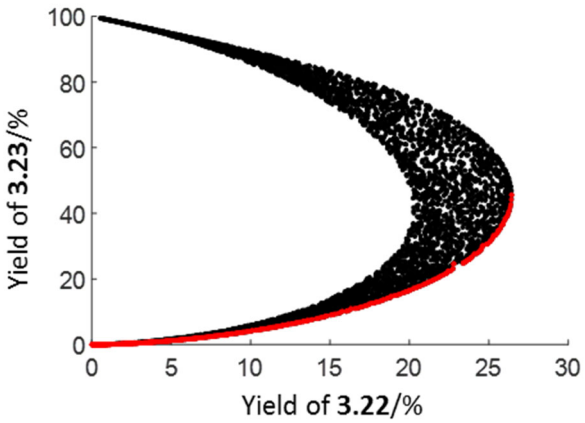


Figure S4. *Graphical representations of the Lactose1 test problem: (i) variable space; (ii) objective space. Black dots = possible solutions, red dots = non-dominated solutions.*

1.5 PK1

(iv)

A_1 = 15.4 M^{-1} min^{-1}, A_2 = 405.2 min^{-1}, $E_{a,1}$ = 12.2 kJ mol^{-1}, $E_{a,2}$ = 20.0 kJ mol^{-1}

$$minimise[-\ln(STY), -\ln(RME)] \quad (5)$$

subject to:

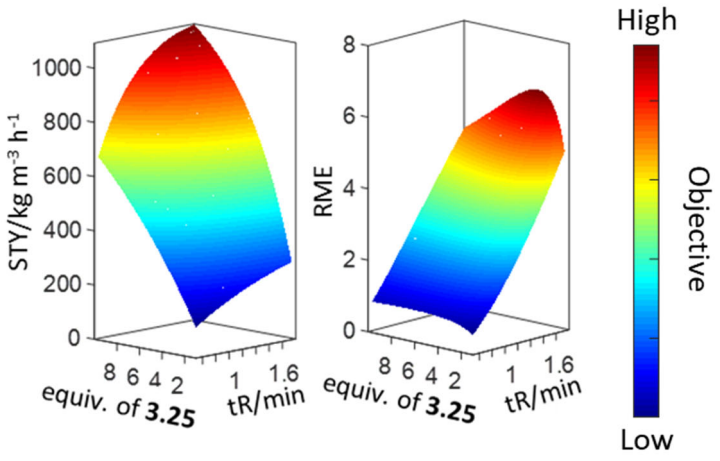
Residence time/min ∈ [0.5, 2]

Equivalents of **3.25** ∈ [1, 10]

Temperature/°C = 50

[**3.24**]/M = 1

(i)



(ii)

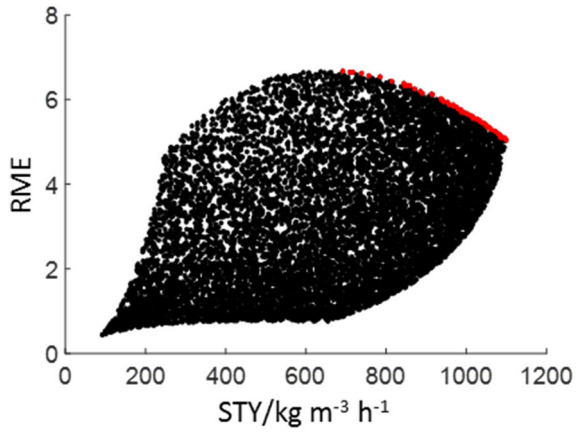


Figure S5. Graphical representations of the PK1 test problem: (i) variable space; (ii) objective space. Black dots = possible solutions, red dots = non-dominated solutions.

1.6 PK2

$$minimise[\ln(\%\ \mathbf{3.26}), -\ln(STY)] \quad (6)$$

subject to:

Residence time/min ∈ [0.5, 2]

Temperature/°C ∈ [25, 150]

Equivalents of **3.25** ∈ [1, 10]

[**3.24**]/M = 1

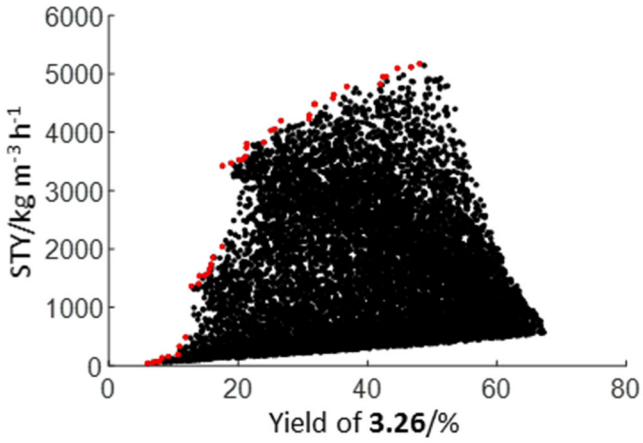


Figure S6. Graphical representations of the objective space for the PK2 test problem. Black dots = possible solutions, red dots = non-dominated solutions.

1.7 Computational Cost

Table S1. Time taken (in seconds) for each algorithm to complete each test problem with a budget of 100 experiments. Simulations were run using an Intel(R) Core(TM) i5-9400 CPU @ 2.90 GHz with 8GB RAM.

		Algorithm				
		TSEMO	**BS-TSEMO**	**NSGA-II**	**ParEGO**	**EIM-EGO**
Test Problem	**VdV1**	697.781	163.298	1.100	120.531	28.577
	S_NAr1	682.188	174.922	2.809	126.039	36.069
	S_NAr2	712.966	178.696	1.902	125.369	39.889
	Lactose1	534.146	139.165	1.514	121.459	29.523
	PK1	545.881	138.971	1.311	121.483	28.597
	PK2	609.808	145.073	1.286	123.045	31.056

2 Algorithm Performance

2.1 Simulator – How it Works

The simulation procedure for each test problem is outlined below. Firstly, the pre-exponential factors, *A*, and activation energies, E_a, are used to calculate the rate constants, *k*, for each step in the reaction using the Arrhenius equation, where *T* = temperature and *R* = gas constant (8.314 J mol^{-1} K^{-1}):

$$k = Ae^{-\frac{E_a}{RT}} \tag{7}$$

The differential rate equations for each step are then solved using an ordinary differential equation (ODE) solver. For example, the differential rate equations for the VdV1 test problem are:

$$rate = -\frac{\Delta A}{\Delta t} = k_1[A] + k_3[A]^2 \tag{8}$$

$$rate = -\frac{\Delta B}{\Delta t} = -k_1[A] + k_2[B] \tag{9}$$

$$rate = -\frac{\Delta C}{\Delta t} = -k_2[B] \tag{10}$$

$$rate = -\frac{\Delta D}{\Delta t} = -k_3[A]^2 \tag{11}$$

In this case, the reactor is modelled as four CSTRs-in-series by solving simultaneously the coupled ODE equations, which are terminated after four reactor volumes to ensure steady-state is simulated. This provides the percentage of each species in the reaction mixture under different sets of conditions, which are subsequently used to calculate the objectives for the given test problem. Random noise inherent with experimental systems is also included by applying a maximum absolute error of 0.25% and maximum relative error of 0.5% to the outputs, where *Y* = yield and *rand* = random number between 0 and 1. If the adjusted yield, Y_{adj}, is less than 0 or greater than 100, then it is forced onto the nearest boundary.

$$Y_{adj} = Y + \left(\left(\frac{rand - 0.5}{2}\right) + Y\left(\frac{rand - 0.5}{100}\right)\right) \tag{12}$$

To compare the performance of the algorithms, the hypervolume is calculated after each iteration, where the hypervolume is defined as the volume between the current Pareto front and a reference point (i.e. larger hypervolume = better Pareto front). The hypervolume is calculated using a Monte-Carlo approximation, which determines the percentage of 100,000 random points in the objective space which are dominated by the current Pareto front. The utopian and anti-utopian point for the objective space of each test problem were selected by creating a superset of the non-dominated solutions from all runs across all algorithms. The reference point for the objective space was then defined as the anti-utopian point shifted by 0.01 of the difference between the utopian and anti-utopian point.

The performance of Thompson sampling efficient multi-objective optimisation (TSEMO), Pareto efficient global optimisation (ParEGO), NSGA-II and expected improvement matrix efficient global optimisation (EIM-EGO) were compared using this approach. Implementations of ParEGO, NSGA-II and EIM-EGO were all available in the platform for evolutionary multi-objective optimisation (PlatEMO) toolbox in MATLAB. An implementation of TSEMO was available on GitHub, and was compared with both one and four points (batch sequential, BS-TSEMO) per iteration. TSEMO, ParEGO and EIM-EGO were all chosen as they represent surrogate model-based multi-objective optimisation algorithms, whereas NSGA-II is a commonly used genetic algorithm. The TSEMO, BS-TSEMO, ParEGO and EIM-EGO were initialised using a LHC design of size 20. Each algorithm had a function evaluation budget of 100, and was ran 20 times for each test problem to compare average performance. To account for the function evaluation budget, the NSGA-II population size and total number of generations were changed to 20 and 5 respectively.

Plots showing the average change in hypervolume throughout the optimisations, and boxplots of the optimisation results after 60 function evaluations are displayed below. These results can be used as benchmarks to compare against other/new multi-objective algorithms.

2.2 Simulator – How to Use

- Software requirements: MATLAB, optimisation toolbox, statistics toolbox.
- To test an algorithm, it must be written in the following format as a .m file:

Inputs:

- data.x = conditions
- data.y = responses
- lowerbounds = lowerbounds of conditions
- upperbounds = upperbounds of conditions
- Opt = algorithm options

Outputs:

- conditions = conditions for next iteration (can contain as many rows as desired)

Example:

```
Opt = TSEMO_options();
conditions = TSEMO(data.x, data.y, lowerbounds, upperbounds, Opt);
```

- Each test problem can be used by running the respective script:
    - VdV1 = VdV1_Test_Problem
    - SnAr1 = SnAr1_Test_Problem
    - SnAr2 = SnAr2_Test_Problem
    - Lactose1 = Lactose1_Test_Problem
    - PK1 = PK1_Test_Problem
    - PK2 = PK2_Test_Problem
- When the script is run, the user is prompted to select the .m file containing the algorithm they want to test.
- The TSEMO algorithm has been included as an example, and can be run by selecting the "TSEMO_example.m" file when prompted.
- The hypervolume is calculated after each experiment, and will be plotted in real-time.
- By default, each test problem will initiate with 20 LHC experiments, and will terminate after an additional 80 experiments have been run by the algorithm (total experiments = 100). These can be adjusted within the test problem scripts by changing the size of the "initial_sample_size" variable and "total_expts" while loop respectively.
- The following optimisation data is stored in the "data" structure:

Data structure:

- data.x = all conditions
- data.y = all natural log transformed responses
- data.z = all untransformed responses
- data.idxs = index of the conditions which have Pareto-optimal solutions
- data.optconds = conditions which have Pareto-optimal solutions
- data.opt = number of Pareto-optimal solutions per iteration
- data.front = Pareto-optimal solutions
- data.hv = hypervolume per iteration

3 Experimental Comparison

3.1 Reactor Setup

Figure S7. Photo of automated flow reactor. Thioanisol being methyl phenyl sulfide.

3.2 Optimisation Procedure

The optimisation procedure is shown algorithmically in Figure S8. An optimisation program was written in Matlab that controlled the pump flow rates and reactor temperature, determined steady state, calculated the responses and controlled the inputs and outputs to and from the TSEMO and EIMEGO algorithm (TSEMO repository: https://github.com/Eric-Bradford/TS-EMO; EIMEGO available in the PlatEMO toolbox: https://github.com/BIMK/PlatEMO). The automated reaction and analysis procedure were designed to consume a minimum amount of material during the optimisations. Firstly, reactant flow rates were reduced to a minimum during heating/cooling of the reactor. Once the reactor reached the desired operating temperature, the reactant flow rates were set to their desired values, and left for 1.7 reactor volumes to reach steady state. Secondly, the initial LHC experiments and the experiments in each iteration were sorted in order of increasing temperature. This avoided unnecessary switches between hot and cold reactions. Finally, sequential experiments were started whilst analysis of the previous experiment was running, except during analysis of the final experiment in the iteration. Hence, the amount of time waiting for analysis was minimized. Optimisations were conducted overnight and manually terminated in the morning under the criterion that a dense front of at least 15 experimental Pareto data points were collected.

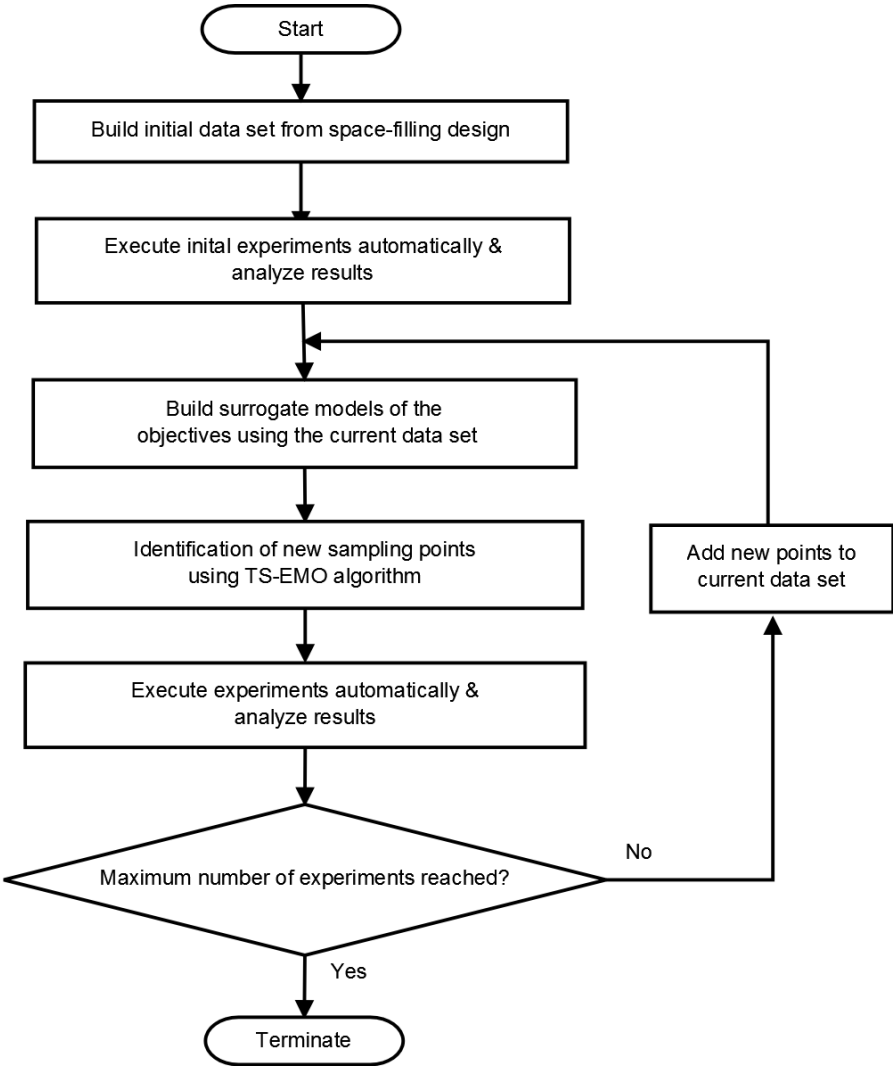


Figure S8. A flowchart of the optimisation procedure.

The responses of each objective were calculated from the GC chromatograms (using the mass spectrum detector) at the end of each iteration, and the results used to update the surrogate models and generate the next set of operating conditions. The objectives were natural log-transformed to enhance the response-surface-based optimisation. As the TSEMO algorithm is a minimizing algorithm, any objectives to be maximized were set to maximize the negative value. The conversion, selectivity and STY were defined as in Equation (13), Equation (14) and Equation (15) respectively, where $\dot{n}_{\text{product}}$ is the molar stream of m-ph-sulfoxide (product), V is the volume of the reactor, t_{res} is the residence time and is the mass of waste.

$$Conversion = 1 - \frac{C_{thioanisol}}{C^0_{thioanisol}} \tag{13}$$

$$\text{Selectivity} = \frac{c_{product}}{C^0_{thioanisol}} \frac{1}{Conversion} \tag{14}$$

$$\text{STY} = \frac{\dot{n}_{product}}{V \times t_{res}} \tag{15}$$

3.3 Characterisation

The section lists flow chemical characterisations and explains why common assumptions could be made in the study.

Residence Time: Is the time a fluid element needs to travel through the capillary. Usually plug flow is assumed, meaning an equal concentration of reagents over the whole tube diameter and no axial back mixing. This enables us to assume that a sample has spent a specific time, x, in the reactor. To prove this assumption a residence time study was performed to show how close to plug flow the system is. Figure S9 shows such a study which was carried out by alternating the concentration of the UV active compound in a step response. The medium time is the average time the fluids element needs to pass the reactor. The change in absorption would be a vertical line if we had an ideal plug flow. In the case of our system deviation from this theoretical line is small enough (Bodenstein numbers were calculated to be above >100 or around 70 tanks-in series). The RTD characterisation experiments were performed for a flow range from 0.5 to 2 ml/min for the given reactor. The residence time distributions were measured by step response. Following Fogler ideal plug flow can be assumed for this high numbers.

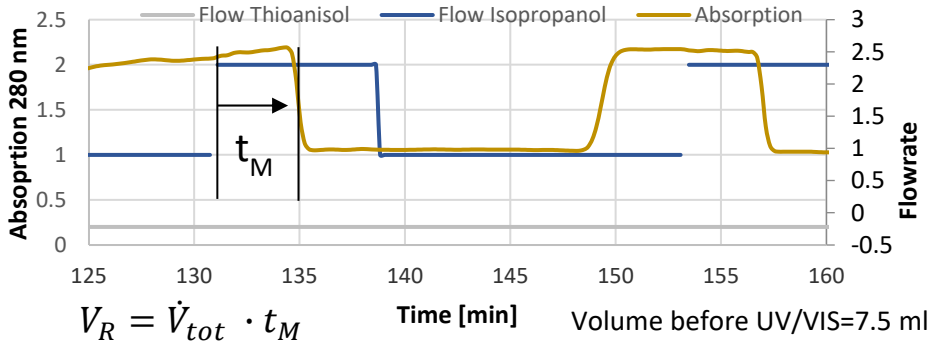


Figure S9. Experimental study of residence time distribution by following the absorption at 280 nm, which is representing methyl phenyl sulfide. While one pump is left on constant flow rate the other is varied to change concentrations and keep the flow stable.

Steady State

This state is reached when there is no change of concentration, temperature or other parameters over time. Both the temperature and the reaction need to have reached steady state conditions before a sample is taken. For an ideal plug flow system the time taken for the reaction to reach steady state is one residence time, but for real flow systems we use a safety margin of 1.5 was taken into account.

Heating & cooling

The reactor is heated using heat cartridges, this takes approximately 20 minutes for a change from 20 to 120 °C. The Eurotherm approaches the set value asymptotically or by overshooting and oscillation (PT1 or PT2 control element). Cooling was achieved by adding a fan for additional air circulation. As the heating element is inside the aluminium block and certain heat losses towards the reaction mix inside the capillary are not avoidable a linear correlation was found from set to actual, measured reaction temperature at the capillary (fit 99.6% accurate over 7 measured evenly spaced points).

$$T_{actual} = 0.83 * T_{set} + 8.38 \quad (16)$$

It is important to incorporate this time in the experimental planning for an optimisation algorithm as clearly both processes add significant time to the experiments.

Reproducibility

For an optimisation to be viable it is essential that the data collected for individual reactions is reproducible, e.g. on three different experimental days experiments performed using the same conditions lead to the same results. Therefore, a study to gauge the reproducibility was performed. Initially, errors in the GC syringe and the reactivity of hydrogen peroxide solution over time were observed. By correcting these flows, by exchanging the syringe and producing fresh solutions daily, the model system achieved reproducibility with less than 10% deviation, see Figure S10.

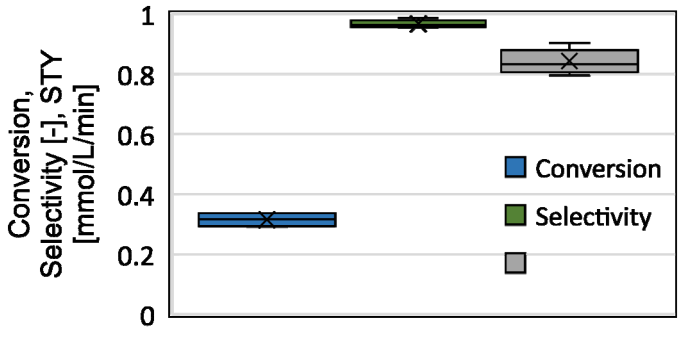


Figure S10. Reproducibility of one experiment with 32% conversion in 6 independent experiments. Parameter are conversion [-], selectivity [-] and space time yield of m-ph-sulfoxide [mmol/L/min].

3.4 Experimental procedures

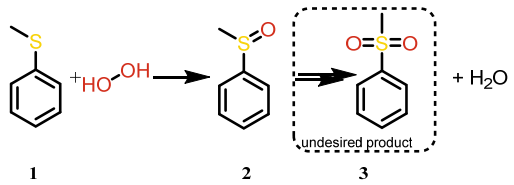


Figure S11. Reaction scheme for methyl phenyl sulfide **1** oxidation to m-ph-sulfoxide **2** and successively m-ph-sulfone **3**.

methyl phenyl sulfide **1** (99%, Fluorochem), Hydrogen peroxide (>30% w/v in H2O, Fischer Chemical), Acetonitrile (99.9%, VWR) and α,α,α-Trifluorotoluene anhydrous (99.%, Alfa Aesar) were purchased from suppliers and used without further purification. Standards of methyl-phenyl-sulfoxide **2** (97%, Sigma-Aldrich) and methyl-phenyl-sulfone **3** (98%, Alfa Aesar) were additionally purchased for calibrations.

Reservoir solutions were prepared by dissolving the desired reagents in solvent under stirring at ambient conditions. Reagent 1 pump: methyl phenyl sulfide (12.4 g, 0.1 mol, 0.4 mol L^{-1}) and trifluorotoluene (3.65 g, 25 mmol) in acetonitrile (235 mL); Reagent 2 pump H_2O_2: hydrogen peroxide (20.4 g, 0.2 mol) in acetonitrile (229.6 mL); Solvent pump for dilution: acetonitrile. The automated reactor was set up according to the schematic shown in Figure 4 in the manuscript, where the reactor

volume = 4 mL and the fixed back pressure = 100 psi, the total experimental volume including the flow cell was 8.5 ml, used for steady state calculations only.

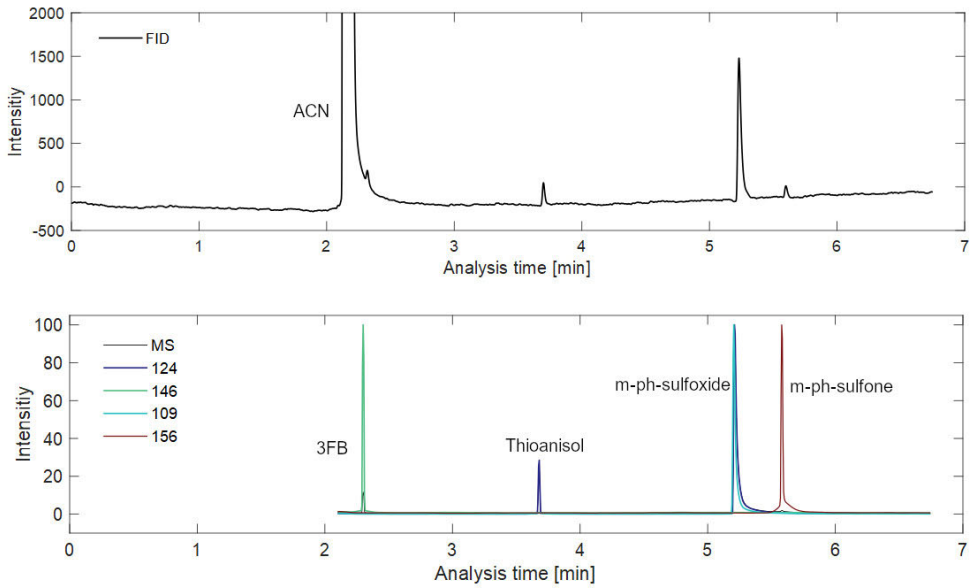


Figure S12. Analytical results adopted from Shimadzu software showing the FID and MS signals in parallel for on experiment (122 °C, 0.1 ml/min Thio, 0.4 ml/min H2O2), thioanisol = methyl phenyl sulfide.

The MS follows each mass during the program, allowing for deconvolution of overlapping signals. Samples were calibrated for methyl phenyl sulfide and reactants with a minimum value of 99.9 obtained for the calibration factor.

Table S2. GC method descriptive parameter used for methyl phenyl sulfide oxidation system. Hydrogen peroxide could not be measured.

Oven Ramp			ion source temperature	200 °C
Rate °C/min	Temp. °C	hold time [min]	interface temperature	250 °C
-	80	0	injection temperature	250 °C
20	215	0	oven temperature	80 °C
MS			injection volume	0.5 µl
Mode selective	140	146	split	100
124	156	109	total program time	**6.75 min**

The self-optimisation was conducted with respect to three-parameters: temperature, pump 1 flow rate thioanisole, pump 2 flow rate hydrogen peroxide. For data analysis the parameters were translated to actual temperature using equation (16), H_2O_2 equivalents and residence time. The parameter limits are shown in Table S3. The objective of the optimisation was to simultaneously maximize Conversion, Selectivity and STY (Equation (17)).

Table S3. Parameter limits for the three-parameter self-optimisation.

Limits	**T/°C**	**Pump Flow 1/ ml/min**	**Pump Flow 2/ ml/min**
Lower	80	0.05	0.05
Upper	150	0.5	0.7
Limits for optimisation analytics	**T_{Actual}/°C**	**H_2O_2 equivalent**	**Residence time/ min**
Lower	77	0.5	4
Upper	133	12	40

minimize [-ln(Conversion), -ln(Selectivity), -ln(STY)] (17)

4 Self-Optimisation Results

4.1 TSEMO

Table S4. Experimental results from the TSEMO optimisation.

Entry	t_{res}/min	H2O2:1	Conc 1/M	Temp/°C	Conversion	Selectivity	STY/mmol L^{-1} min^{-1}
1	7.80	7.33	0.05	122.31	0.37	0.95	0.26
2	7.67	1.50	0.19	130.63	0.19	1.00	0.38
3	5.91	1.89	0.08	128.15	0.60	0.83	1.98
4	6.37	7.46	0.00	122.33	1.00	0.89	1.15
5	17.33	5.55	0.01	119.90	0.89	0.90	0.07
6	10.51	0.80	0.11	116.70	0.60	0.96	0.57
7	12.70	3.32	0.09	113.58	0.43	1.00	0.13
8	8.95	10.71	0.06	108.40	0.00	0.28	0.00
9	15.12	0.68	0.24	104.06	0.20	0.91	0.06
10	5.14	2.88	0.13	98.86	0.20	1.00	0.99
11	6.73	4.33	0.10	95.37	0.19	0.91	0.29
12	6.16	4.15	0.10	92.09	0.24	0.48	0.25
13	10.24	5.11	0.10	89.91	0.13	1.00	0.05
14	7.22	2.39	0.14	86.37	0.25	0.78	0.38
15	9.80	3.44	0.15	79.22	0.00	0.00	0.00
16	11.64	0.97	0.27	76.89	0.00	0.00	0.00
17	7.84	7.53	0.06	122.31	0.32	0.97	0.21
18	6.80	1.50	0.05	133.30	0.77	0.96	2.15
19	7.50	5.58	0.11	75.00	0.00	0.00	0.00
20	7.29	8.69	0.00	128.14	0.98	0.91	0.69
21	7.02	4.55	0.11	82.32	0.12	0.89	0.15
22	6.52	8.79	0.06	82.36	0.14	0.46	0.07
23	9.25	7.28	0.05	97.11	0.47	0.91	0.19
24	8.05	1.00	0.26	85.70	0.02	0.89	0.04
25	7.57	1.56	0.17	116.04	0.24	0.98	0.48
26	38.25	1.83	0.15	79.94	0.26	0.98	0.00
27	9.10	0.51	0.15	107.51	0.52	0.92	0.81
28	9.18	0.91	0.11	125.19	0.58	0.74	0.61
29	7.84	0.53	0.20	122.31	0.36	0.98	0.93
30	5.60	1.61	0.18	126.48	0.19	0.66	0.64
31	5.40	2.28	0.18	85.65	0.01	0.91	0.06
32	9.83	0.35	0.34	119.69	0.00	0.28	0.00
33	7.40	7.69	0.04	110.64	0.47	0.90	0.35
34	5.54	3.43	0.10	122.53	0.31	0.97	1.03
35	5.57	2.61	0.17	128.40	0.00	0.28	0.00
36	6.99	13.76	0.05	93.18	0.00	0.00	0.00
37	12.10	0.66	0.30	77.22	0.00	0.00	0.00
38	8.24	1.35	0.21	121.65	0.12	0.86	0.18
39	5.57	3.29	0.12	103.10	0.23	0.98	0.80
40	7.51	1.85	0.20	125.36	0.04	0.92	0.07
41	6.82	2.47	0.14	89.93	0.21	0.97	0.46

42	7.73	2.28	0.17	115.36	0.08	0.94	0.12
43	7.66	2.97	0.07	93.07	0.54	0.97	0.74
44	10.55	13.16	0.01	109.83	0.87	0.73	0.11
45	16.47	1.80	0.21	126.21	0.00	0.00	0.00
46	6.19	4.73	0.07	103.66	0.38	0.98	0.75
47	15.13	1.33	0.23	114.36	0.02	1.00	0.01
48	6.24	6.72	0.09	90.93	0.01	0.94	0.01
49	19.85	2.59	0.06	119.67	0.66	0.76	0.04
50	13.53	1.75	0.20	129.39	0.08	0.69	0.02
51	13.45	2.22	0.09	132.79	0.53	0.98	0.16

4.2 EIMEGO

Table S5. Experimental results from the EIMEGO optimisation.

Entry	t_{res}/min	H2O2:1	Conc 1/M	Temp/°C	Conversion	Selectivity	STY/mmol L^{-1} min^{-1}
1	7.80	7.33	0.05	122.31	0.37	0.95	0.26
2	7.67	1.50	0.19	130.63	0.19	1.00	0.38
3	5.91	1.89	0.08	128.15	0.60	0.83	1.98
4	6.37	7.46	0.00	122.33	1.00	0.89	1.15
5	17.33	5.55	0.01	119.90	0.89	0.90	0.07
6	10.51	0.80	0.11	116.70	0.60	0.96	0.57
7	12.70	3.32	0.09	113.58	0.43	1.00	0.13
8	8.95	10.71	0.06	108.40	0.00	0.28	0.00
9	15.12	0.68	0.24	104.06	0.20	0.91	0.06
10	5.14	2.88	0.13	98.86	0.20	1.00	0.99
11	6.73	4.33	0.10	95.37	0.19	0.91	0.29
12	6.16	4.15	0.10	92.09	0.24	0.48	0.25
13	10.24	5.11	0.10	89.91	0.13	1.00	0.05
14	7.22	2.39	0.14	86.37	0.25	0.78	0.38
15	9.80	3.44	0.15	79.22	0.00	0.00	0.00
16	11.64	0.97	0.27	76.89	0.00	0.00	0.00
17	9.92	1.04	0.06	122.31	0.32	0.97	0.21
18	8.87	5.61	0.49	114.72	0.00	0.00	0.00
19	6.47	7.62	0.04	127.86	0.74	0.97	0.43
20	7.24	2.29	0.09	118.67	0.19	0.93	0.22
21	7.73	7.59	0.30	109.88	0.00	0.28	0.00
22	8.11	1.56	0.05	120.10	0.56	0.81	0.33
23	8.12	3.43	0.08	129.39	0.79	0.93	1.23
24	6.98	5.02	0.16	88.70	0.30	0.82	0.27
25	13.20	3.05	0.00	131.10	0.98	0.90	1.19
26	7.52	2.97	0.00	113.33	1.00	0.87	0.24
27	17.35	2.41	0.22	85.78	0.13	1.00	0.19
28	9.88	1.67	0.00	112.08	0.99	0.91	0.12
29	8.54	1.07	0.15	122.43	0.61	0.97	0.53
30	14.03	2.29	0.43	117.59	0.11	0.98	0.17
31	7.64	12.74	0.00	132.60	1.00	0.79	0.21
32	6.04	1.93	0.00	130.53	0.99	0.87	0.42

33	9.63	0.96	0.34	77.11	0.02	0.92	0.06
34	9.64	1.83	0.38	128.67	0.26	0.99	0.32
35	7.82	8.00	0.15	132.50	0.57	0.98	0.52
36	9.22	9.60	0.10	78.19	0.08	0.96	0.05
37	4.80	2.90	0.04	129.89	0.58	0.91	0.18
38	7.47	4.48	0.25	84.12	0.01	1.00	0.08
39	15.16	8.03	0.11	124.30	0.39	0.97	0.45
40	5.44	4.03	0.04	95.99	0.67	0.97	0.06
41	9.97	0.50	0.20	132.55	0.01	0.95	0.03
42	16.37	1.65	0.49	89.04	0.26	0.98	0.33
43	10.31	8.27	0.28	112.28	0.26	0.99	0.05
44	12.12	1.83	0.10	100.75	0.09	0.99	0.02
45	11.79	1.06	0.31	124.61	0.13	0.99	0.06
46	21.47	2.83	0.14	122.64	0.72	0.96	0.44
47	6.35	1.97	0.25	129.53	0.05	0.96	0.00
48	5.83	3.11	0.28	79.19	0.18	0.99	0.56
49	6.28	2.02	0.14	128.84	0.42	0.98	1.30
50	10.91	1.14	0.30	132.64	0.08	0.99	0.26
51	8.85	0.94	0.43	105.95	0.07	0.99	0.05
52	7.66	6.17	0.37	117.73	0.28	0.98	0.43
53	9.92	1.04	0.09	112.60	0.39	0.99	0.33

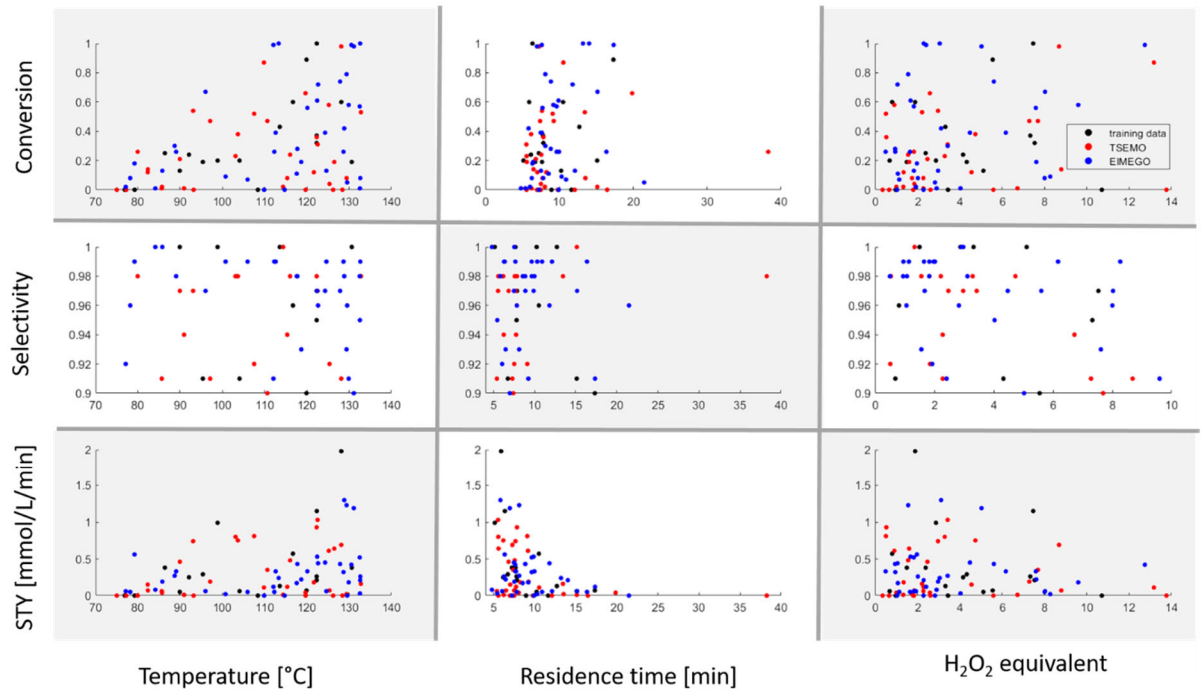


Figure S13. Experimental overview for all interaction between input and optimisation parameter.

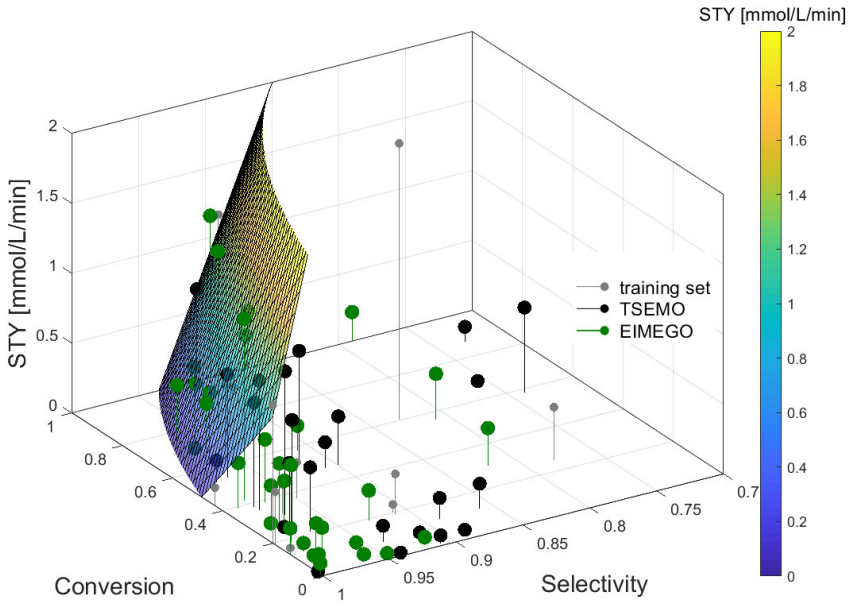


Figure S14. *Approximated 3-dimensional Pareto front and experimental data near it.*

Conversion, Selectivity and STY of **2** were optimised against each other. As a 3-dimensional system the visualizations cannot represent the freedom in one of the three optimisation criteria. Pareto front was estimated via polynomial fitting using the non-dominated solutions using an x^2y^1 model for f = STY(Conversion, Selectivity).

4.3 Hyperparameters, GP Surrogate Models and Simulation

Hyperparameters

The hyperparameters can be extracted from the surrogate models built during the optimisation to reveal important process information. For the hyperparameters of the input variables (Θ_i) a lower value indicates a greater contribution to the output. The σ_n^2 hyperparameter corresponds to the noise of the system, which is medium low for the objectives in both algorithm studies. This indicates high quality and consistent data.

Table S6. Overview Hyperparameters for TSEMO and EIMEGO.

	TSEMO		
Variable	GP 1 (Conversion)	GP 2 (Selectivity)	GP 3 (STY)
$\Theta_{\text{temperature}}$	1.27	-1.83	-1.15
$\Theta_{\text{residence time}}$	-3.23	0.11	-1.87
$\Theta_{\text{H2O2e eq.}}$	-2.75	0.79	-2.74
σ_n^2	3.77×10^{-2}	1.62×10^{-1}	2.43×10^{-2}
	EIMEGO		

Variable	GP 1 (STY)		GP 2 (% impurity)
$\Theta_{\text{temperature}}$	-2.90	-2.51	-2.78
$\Theta_{\text{residence time}}$	-1.69	-1.91	-1.64
$\Theta_{\text{H2O2e eq.}}$	1.48	3.30	3.29
σ_n^2	6.54×10^{-2}	1.07×10^{-1}	7.09×10^{-2}