Incorporating Digitalization and Automation in the Development of Flow Processes for API Synthesis

Jason D. Williams

Center for Continuous Flow Synthesis and Processing (CCFLOW), RCPE GmbH and Institute of Chemistry, University of Graz, Austria

Jason.williams@rcpe.at http://ccflow.at

TU Graz UNI GRAZ JOANNEUM RESEARCH / Federal Ministry Republic of Austria Climate Action, Environmen Energy, Mobility, Innovation and Technology Federal Ministry Republic of Austria Labour and Economy FFG Promoting Innovation. / Das Land Steiermark Wirtschaft, Tourismus, Regionen, Wissenschaft und Forschung SFG NEUES DENKEN. NEUES FÖRDERN.

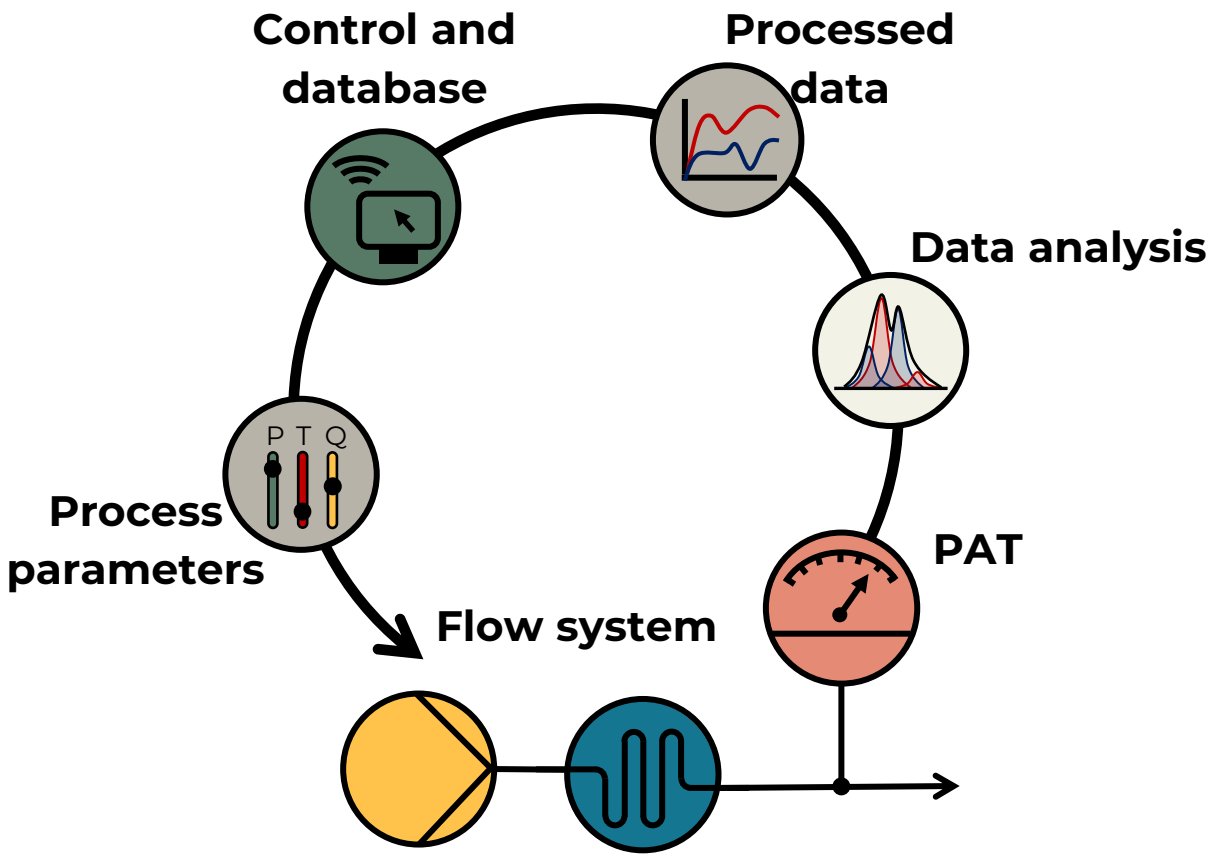
Introduction

Autonomous Flow Chemistry Platform

Why?

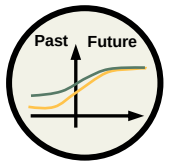
- Free up chemist resource
- Data-rich experimentation at an early development stage
- More than “just” finding optimal lab scale conditions
  - Process understanding
  - Kinetic model generation
  - Reactor/flow characterization
  - Preliminary control approaches
- Faster/easier scale-up and control definition!

How?



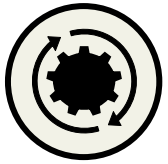
Initial 3-PAT reactor platform: Sagmeister, P. et al. *React. Chem. Eng.* **2019**, *4*, 1571
Full PAT integration: Sagmeister, P. et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 8139

Autonomous Flow Chemistry Platform



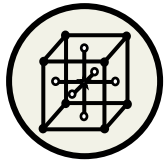
Model Predictive Control (MPC)

Sacher, S. et al. *Chem. Eng. Res. Des.* **2022**, *177*, 493



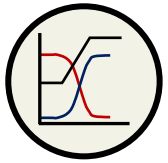
Self-Optimization

Sagmeister, P. et al. *Adv. Sci.* **2022**, *9*, 2105547



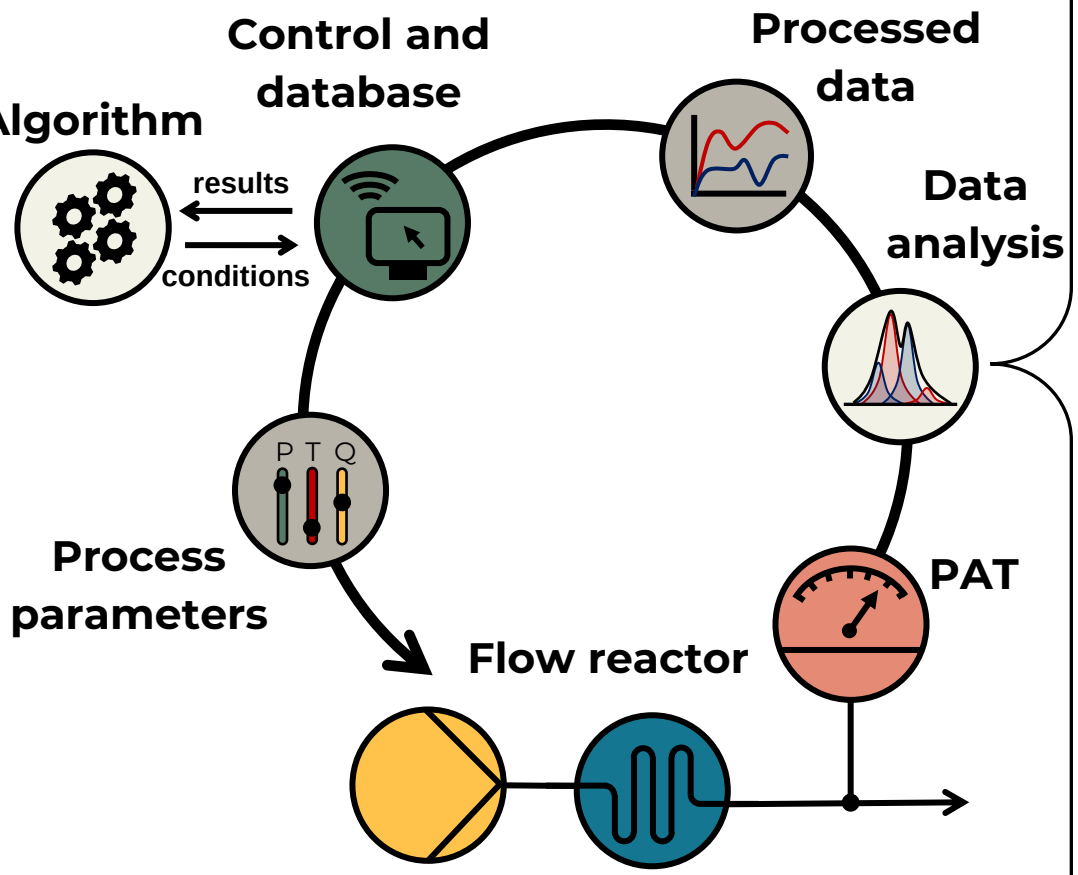
Iterative Model Building

Knoll, S. et al. *React. Chem. Eng.* **2022**, *7*, 2375



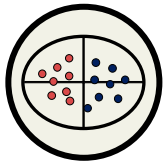
Dynamic Experiments

Sagmeister, P. et al. *Manuscript in preparation*



Integration

Sagmeister, P. et al. *React. Chem. Eng.* **2019**, *4*, 1571

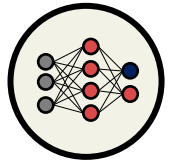


Partial Least Squares (PLS)

Sagmeister, P. et al. *React. Chem. Eng.* **2020**, *5*, 677

Indirect Hard Modeling (IHM)

Sagmeister, P. et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 8139



Artificial Neural Network (ANN)

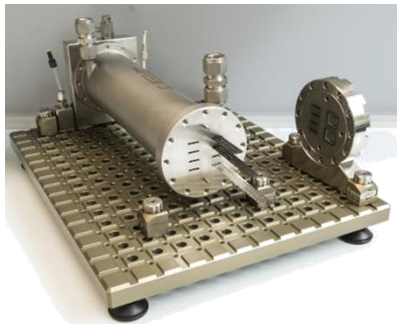
Sagmeister, P. et al. *Digital Discov.* **2022**, *1*, 405

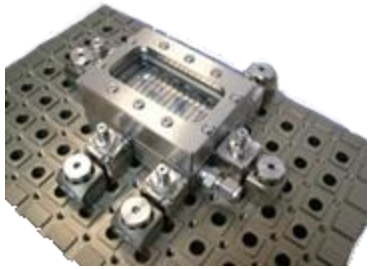
2

Model Predictive Control

MPC for API Synthesis

Reaction and Analysis Strategy



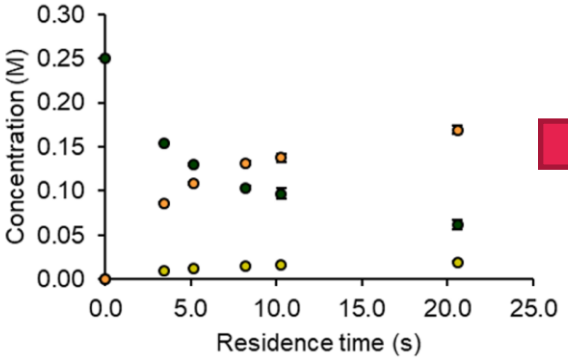


Sagmeister, P. et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 8139

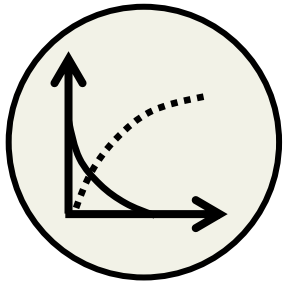
MPC for API Synthesis

Hybrid Reaction Model – Training Workflow

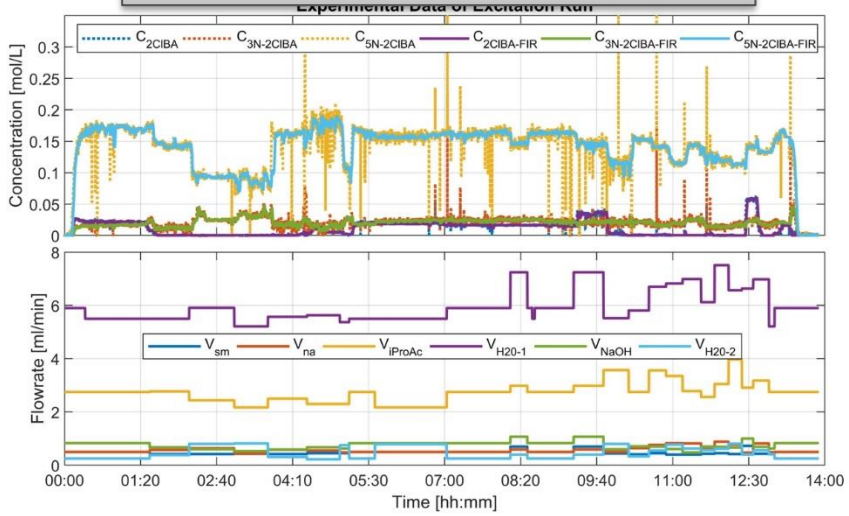
Data from kinetic experiments and DoE



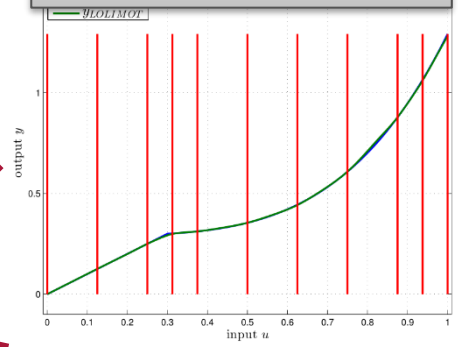
Kinetic models



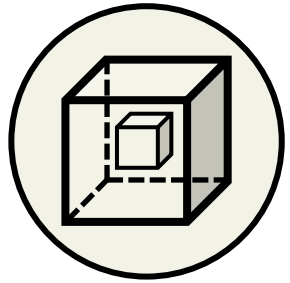
Experimental "excitation" data

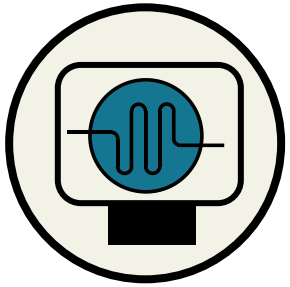


LoLiMoT training (machine learning)



Neuro-Fuzzy hybrid reaction models

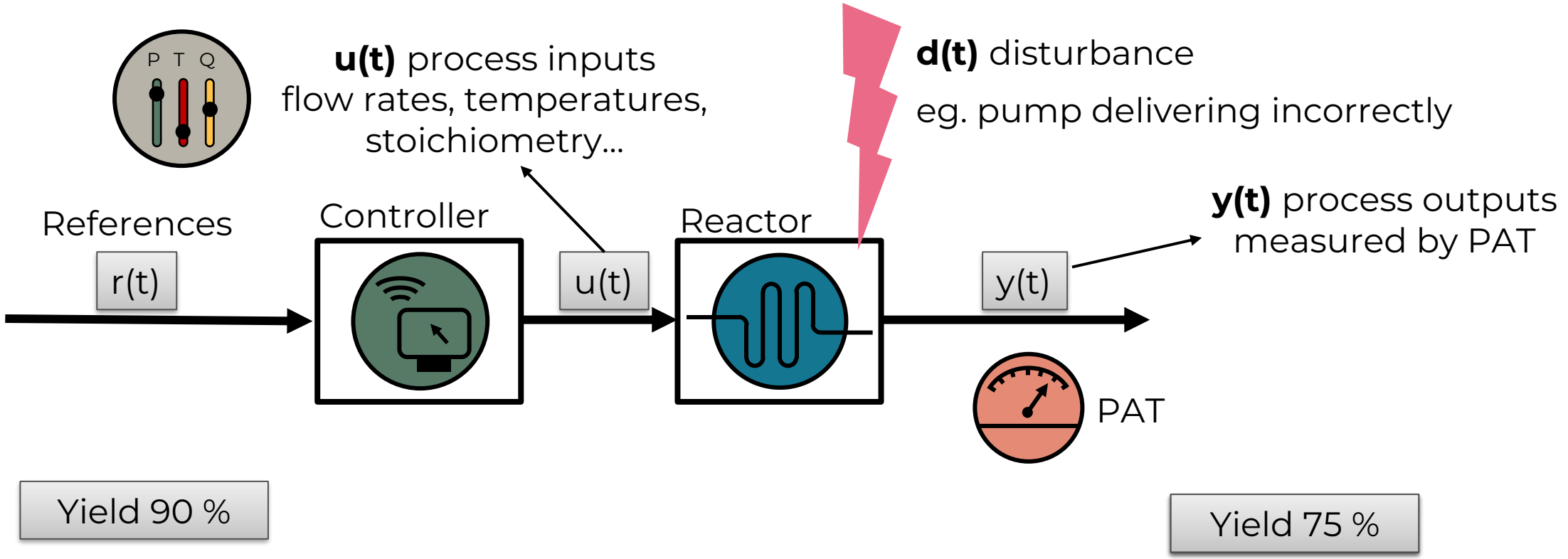




Digital twin

MPC for API Synthesis

Automated Process Control Scheme

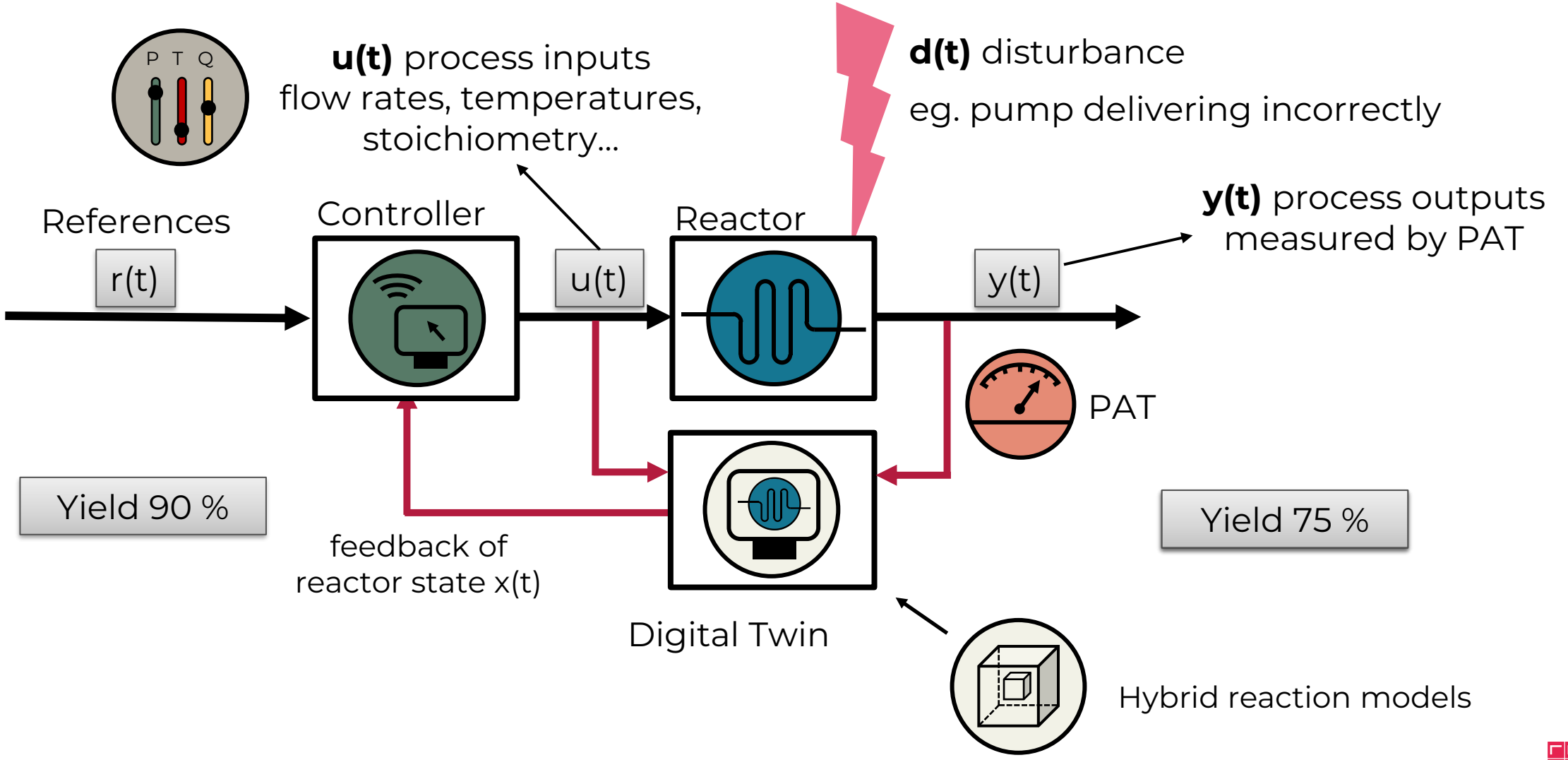


ideal case r(t) = y(t)

What happens if we have a disturbance?

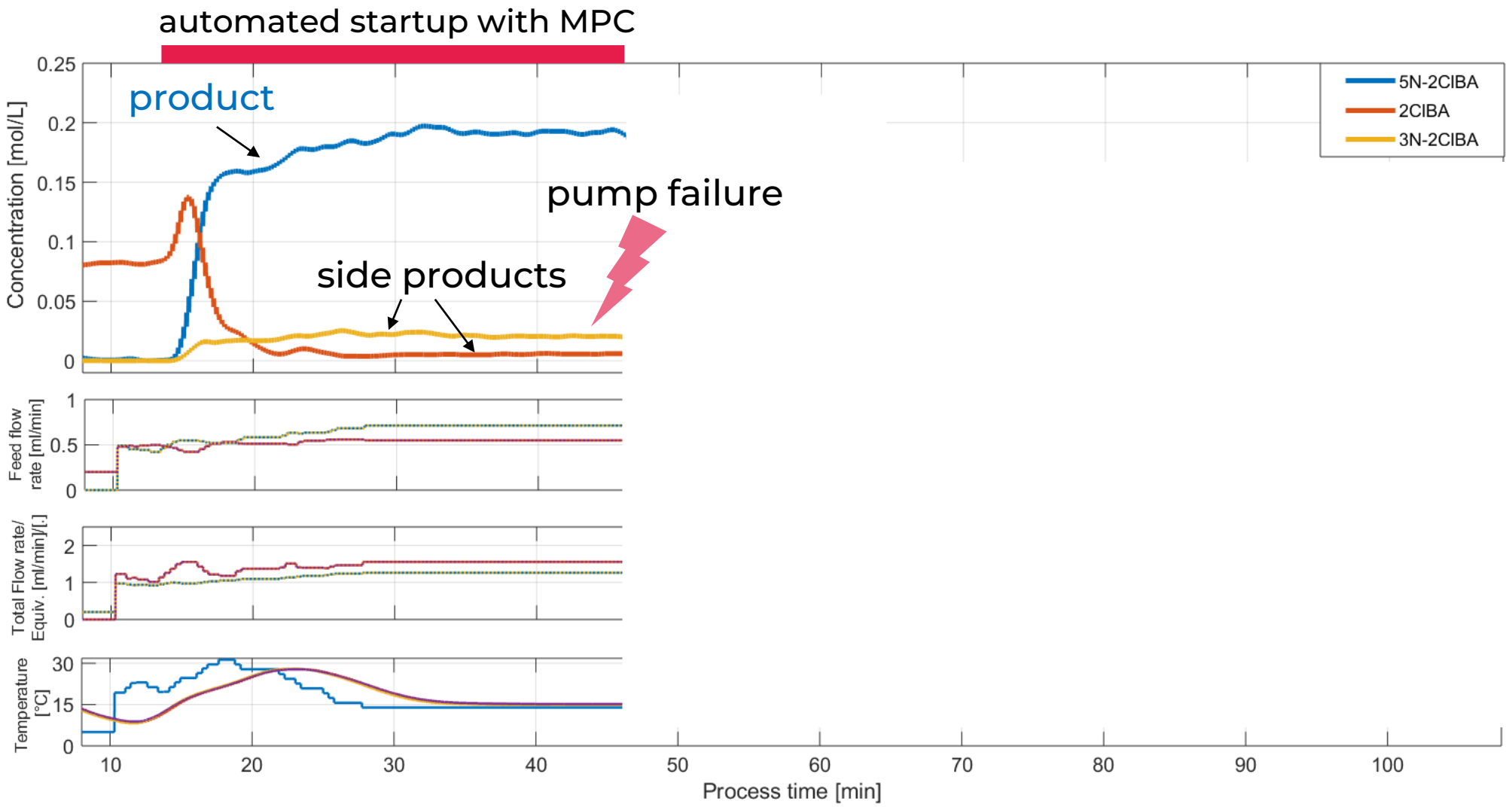
MPC for API Synthesis

Automated Process Control Scheme



MPC for API Synthesis

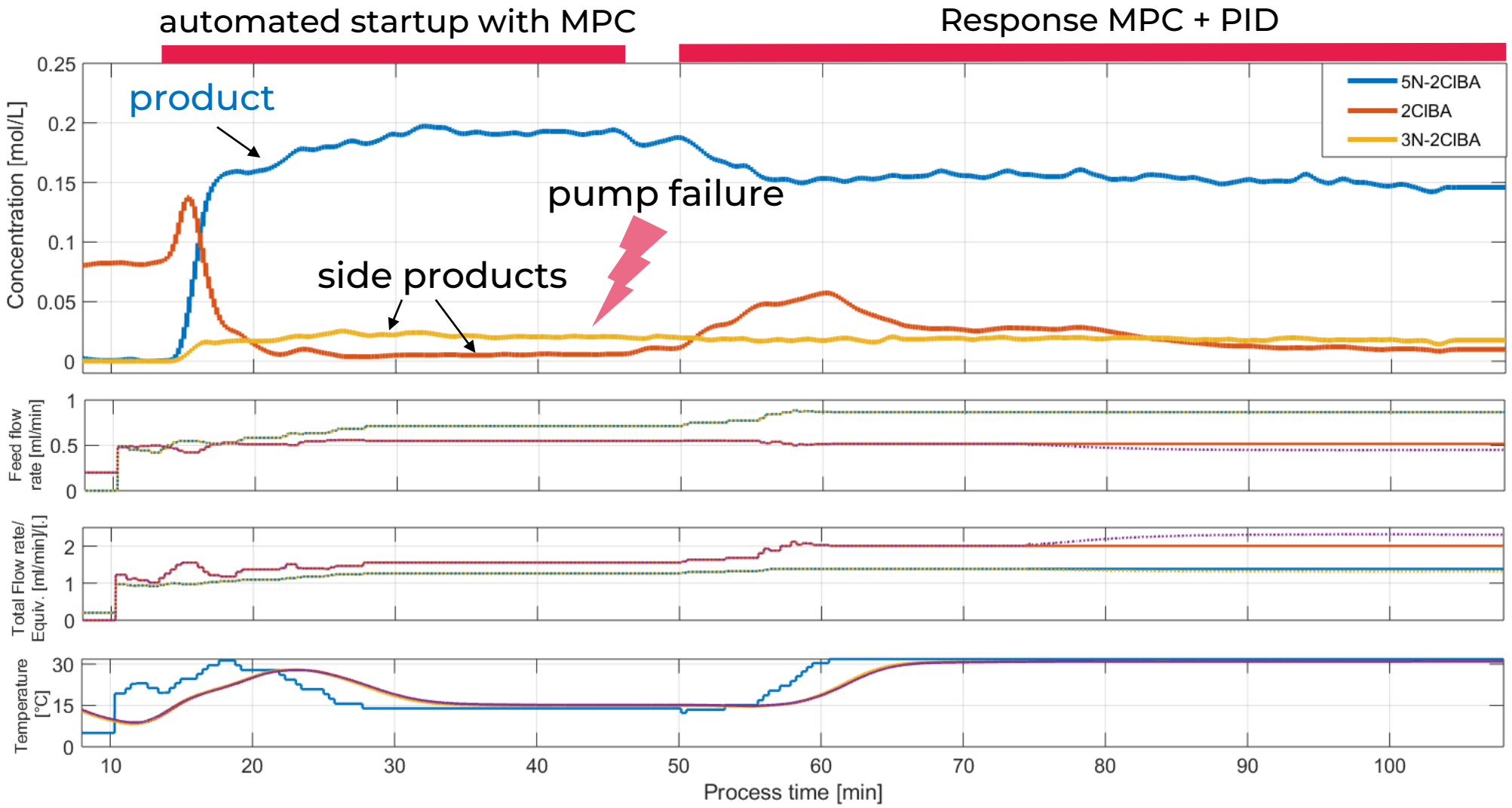
Example Experimental Data



Sacher, S. et al. *Chem. Eng. Res. Des.* **2022**, *177*, 493

MPC for API Synthesis

Example Experimental Data

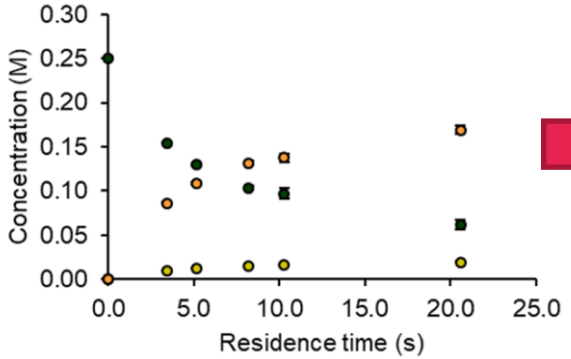


Sacher, S. et al. *Chem. Eng. Res. Des.* **2022**, *177*, 493

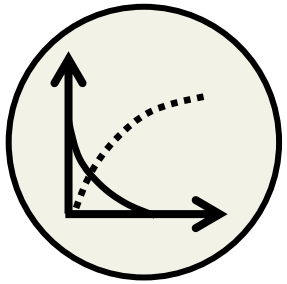
MPC for API Synthesis

Hybrid Reaction Model – Training Workflow

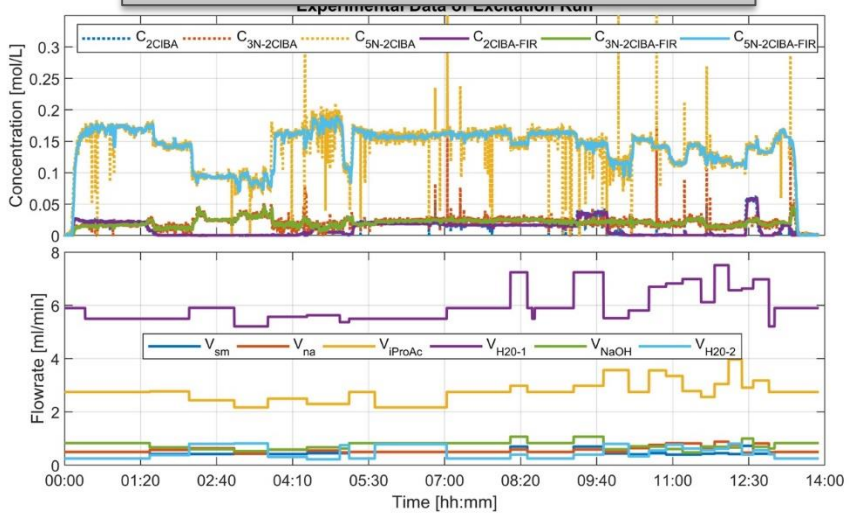
Data from kinetic experiments and DoE



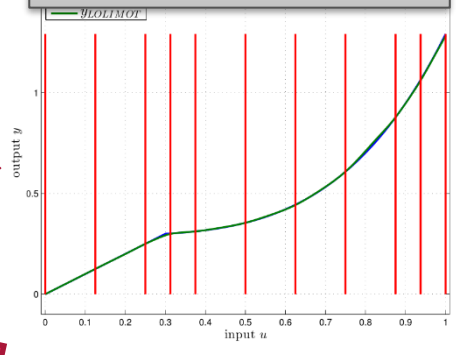
Kinetic models



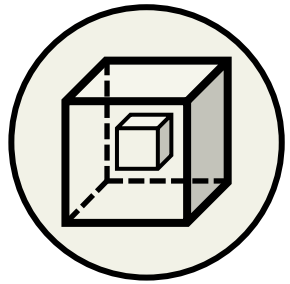
Experimental "excitation" data

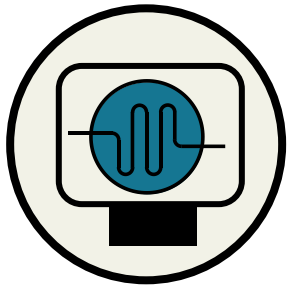


LoLiMoT training (machine learning)



Neuro-Fuzzy hybrid reaction models

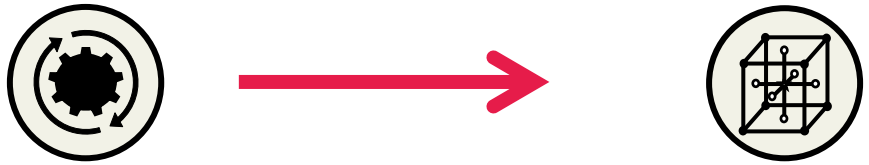




Digital twin

Model-Building in a Data-Rich Environment

Approach 1: Empirical Models



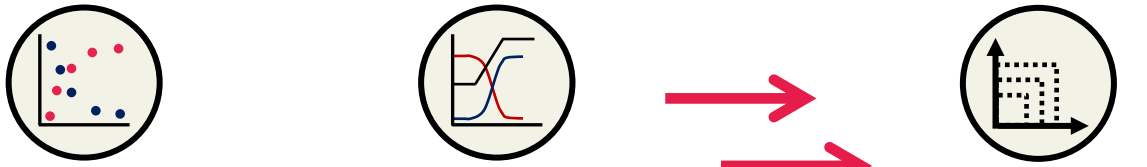
Self-Optimization

- Broad process space
- Multiple objectives

Reaction Model

- Around the optimum
- Automated DoE

Approach 2: Kinetics-based Models

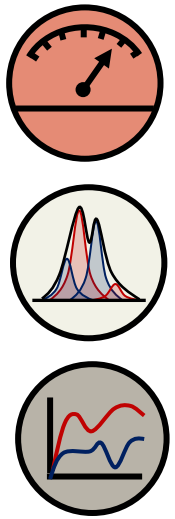


Steady-State Experiments

Dynamic Experiments

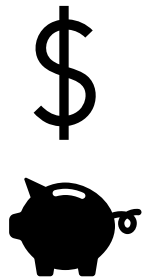
Scale-up

- Building a kinetic model
- Reactor characterization



PAT and Data Analysis

- High data density
  - NMR, FTIR, Raman
- Identify trace impurities
  - Chromatography
- Identify mechanism



Cost of Optimization

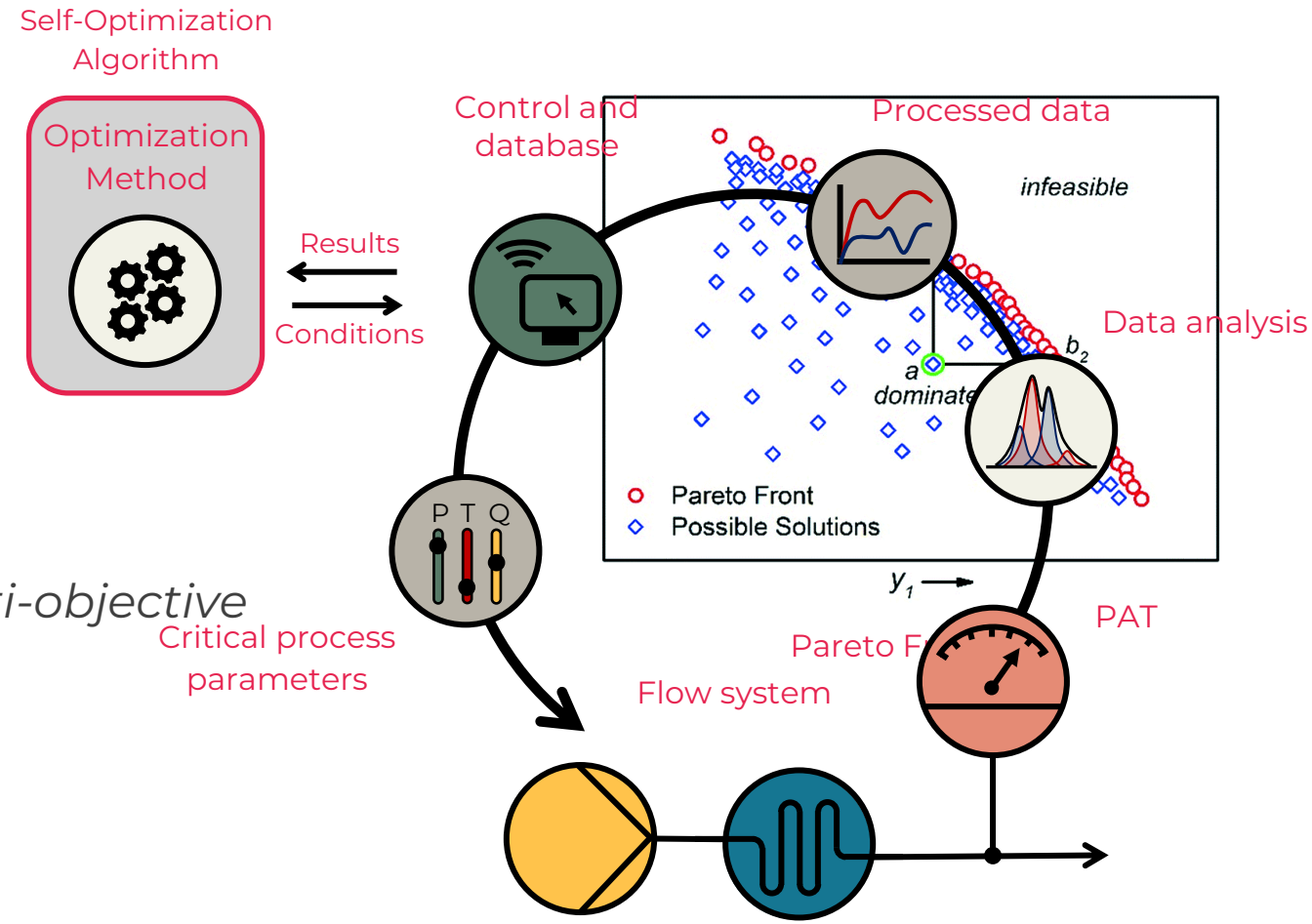
- Material consumption
  - Droplet-Flow reactor
- Automation
- Minimal effort for operator

3

Multi-Step Self-Optimization

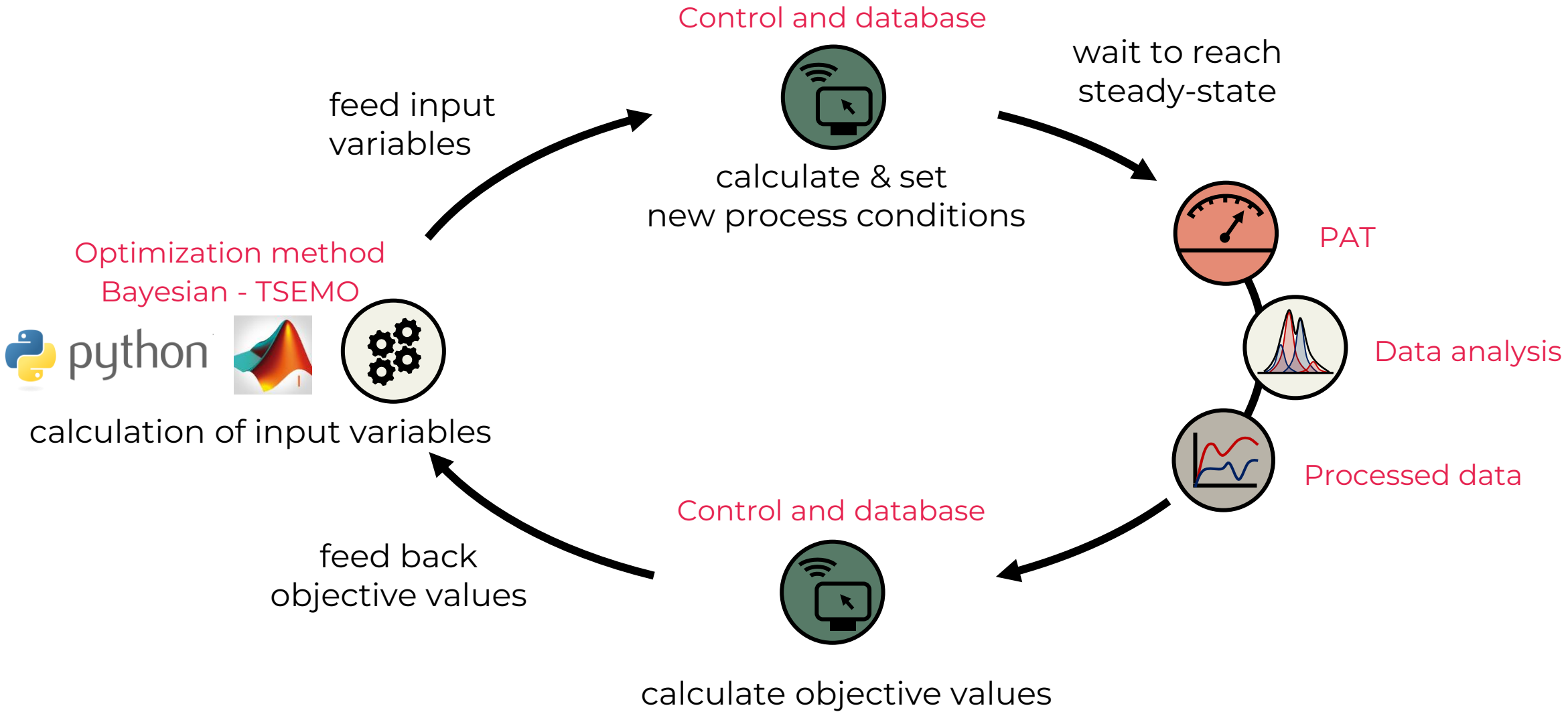
Self-Optimization Algorithms

- Work as **“Black Box”** or **“Grey Box”**
  - Cover large design space
  - No prior chemistry knowledge
- Single- or Multi-Objective
- TSEMO
  - *Thompson sampling efficient multi-objective optimization algorithm*
  - Global, multi-objective algorithm



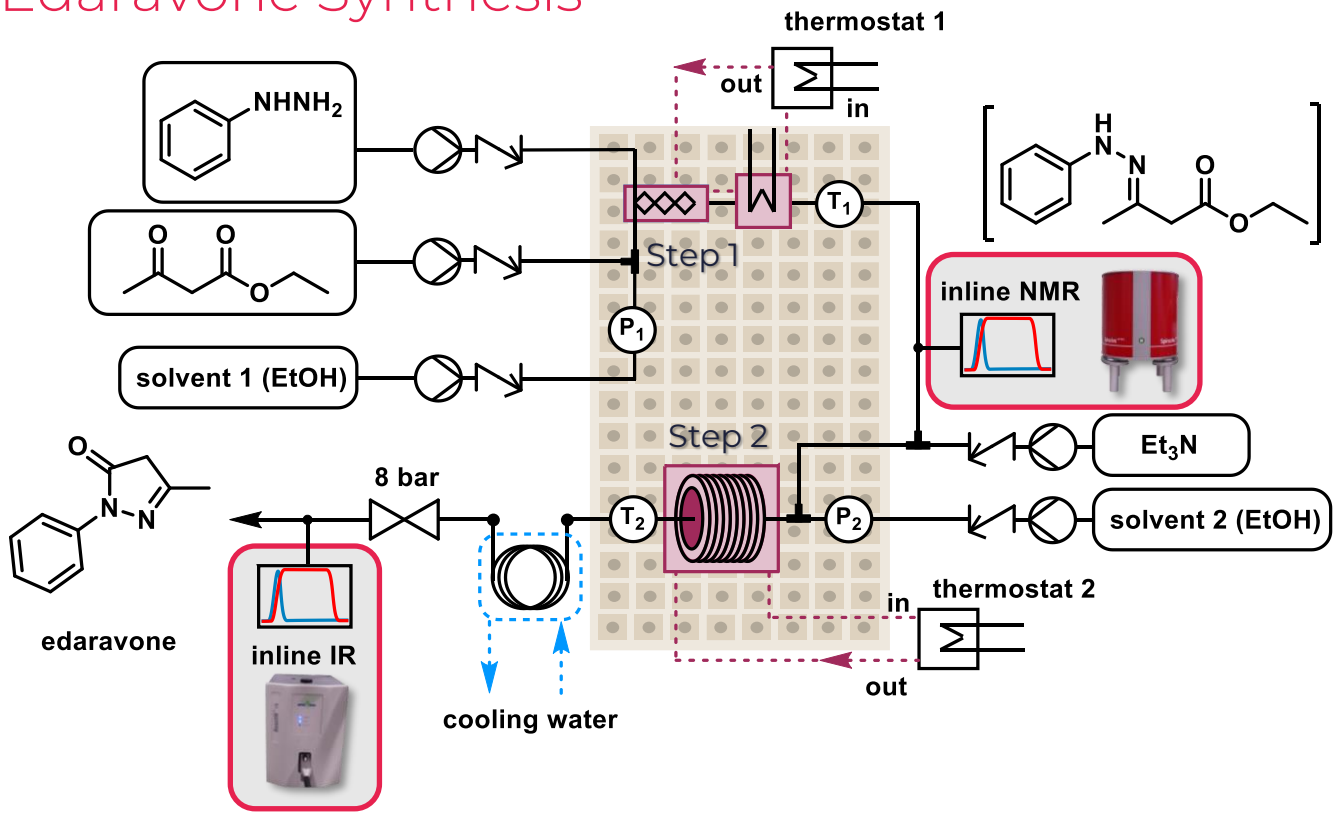
Clayton, A. D. et al. *React. Chem. Eng.* **2019**, *4*, 1545
Bradford, E. et al. *J. Glob. Optim.* **2018**, *71*, 407

Self-Optimization Workflow

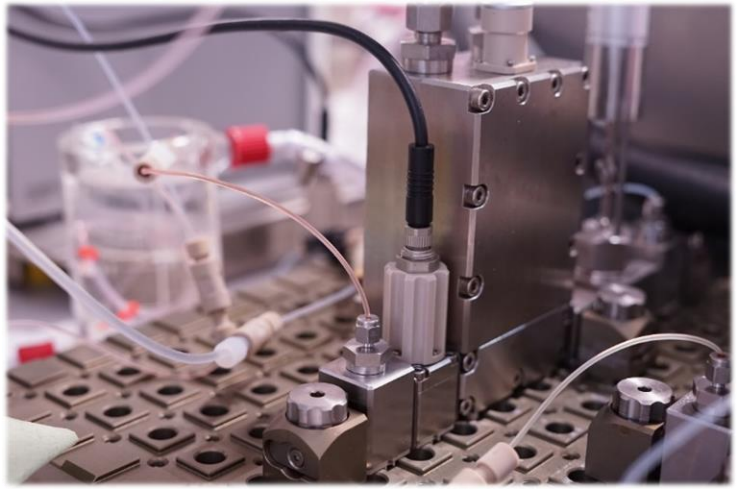


Reaction Setup

Edaravone Synthesis



Cascade Mixer (Step 1)



Capillary Reactor (Step 2)

- Synthesis of a simple API (2 steps)
- Liquid starting materials and no solubility concerns
- Separation of steps to improve selectivity

Zhou, S. et al. *Org. Process Res. Dev.* **2021**, *25*, 2146

Optimization Objectives and Variables

Three Objectives

↑ Yield of Intermediate
STEP 1

↓ Reagent Consumption
STEP 1 & STEP 2

↑ Space-Time Yield
STEP 2

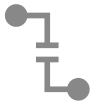
Seven Variables

STEP 1

Residence Time
0.5 – 1.5 min

Concentration
1.0 – 2.4 M

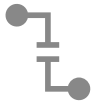
Temperature
10 – 50 °C



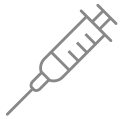
Phenylhydrazine Equivalents
0.5 – 1.5 eq.

STEP 2

Temperature
25 – 130 °C



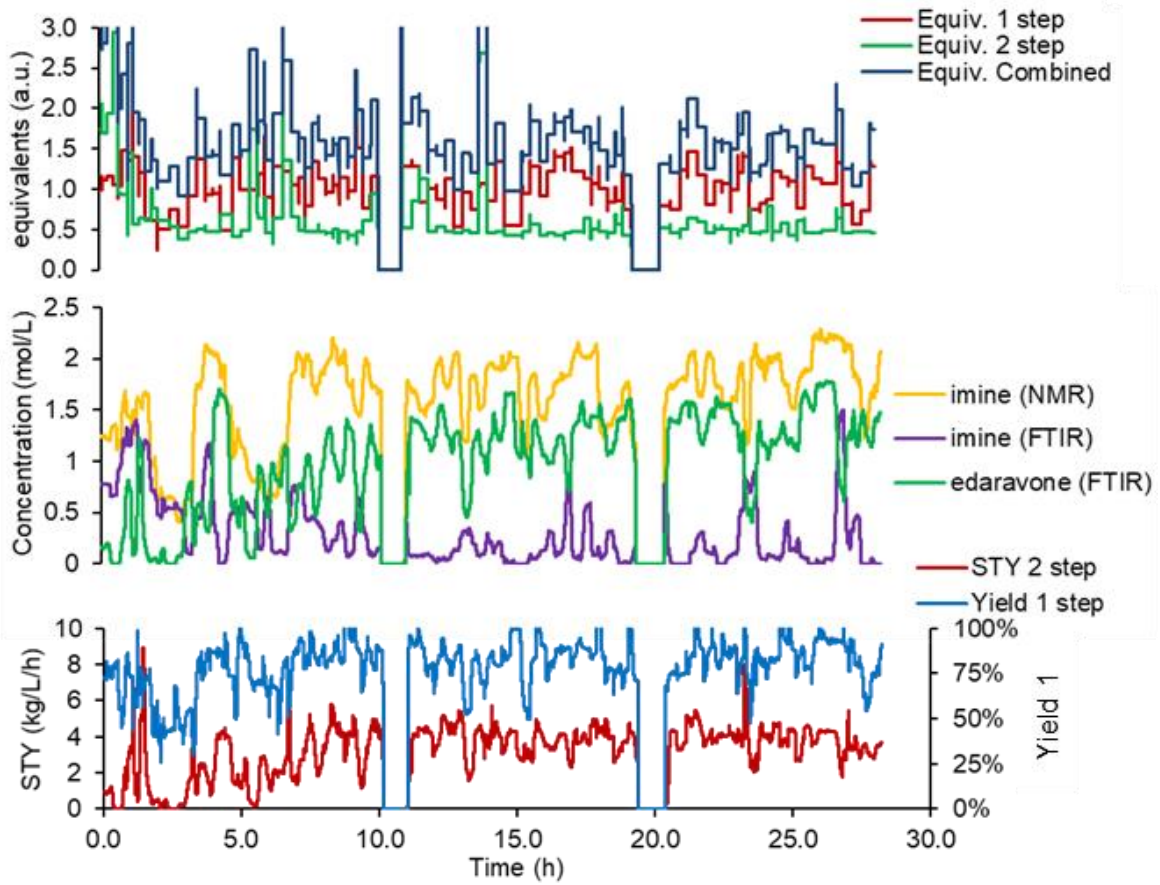
Triethylamine Equivalents
0.5 – 3.0 eq.



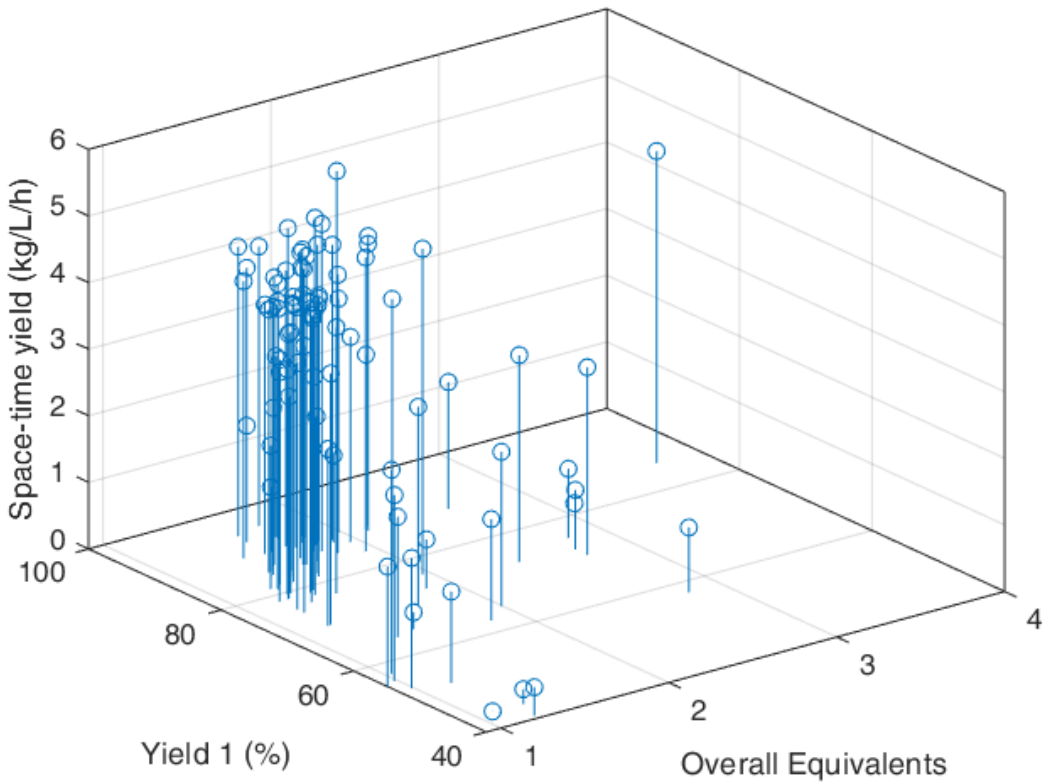
Dilution
0 – 1 x Q_1

Multi-Step Optimization Results

Continuous Data



Objectives



85 optimization experiments (26 h)

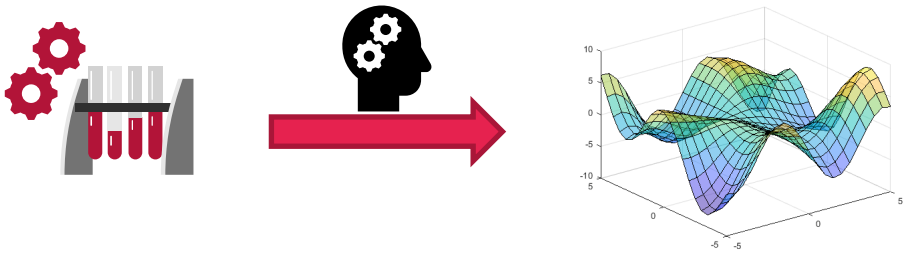
Yield 1 step: > 95%, STY: 5.42 kg L^{-1} h^{-1}

4

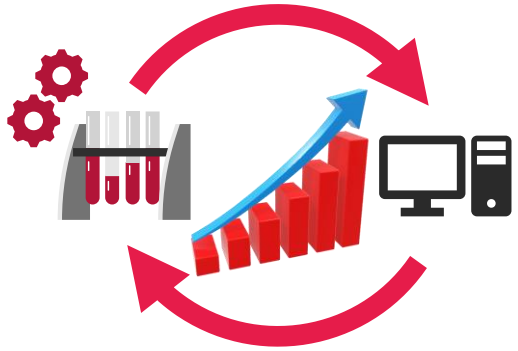
Iterative Model Building

Iterative Model Building Concept

State-of-the-Art



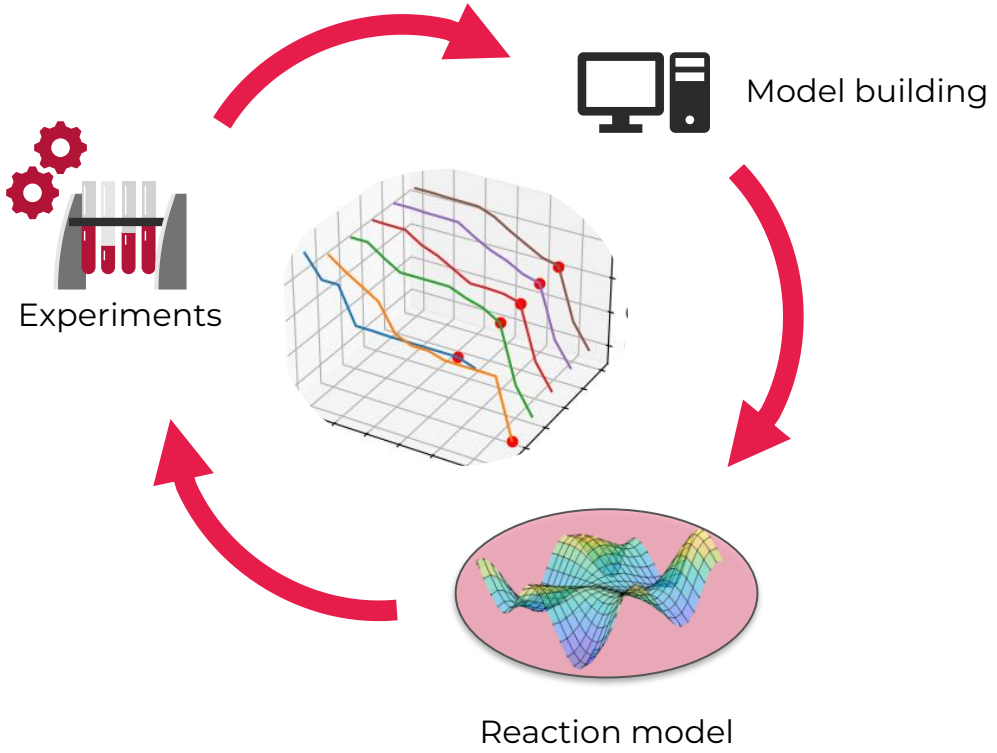
Automated experiments with offline model building



Autonomous optimization without detailed models

Our Aim

Fully automated iterative model building

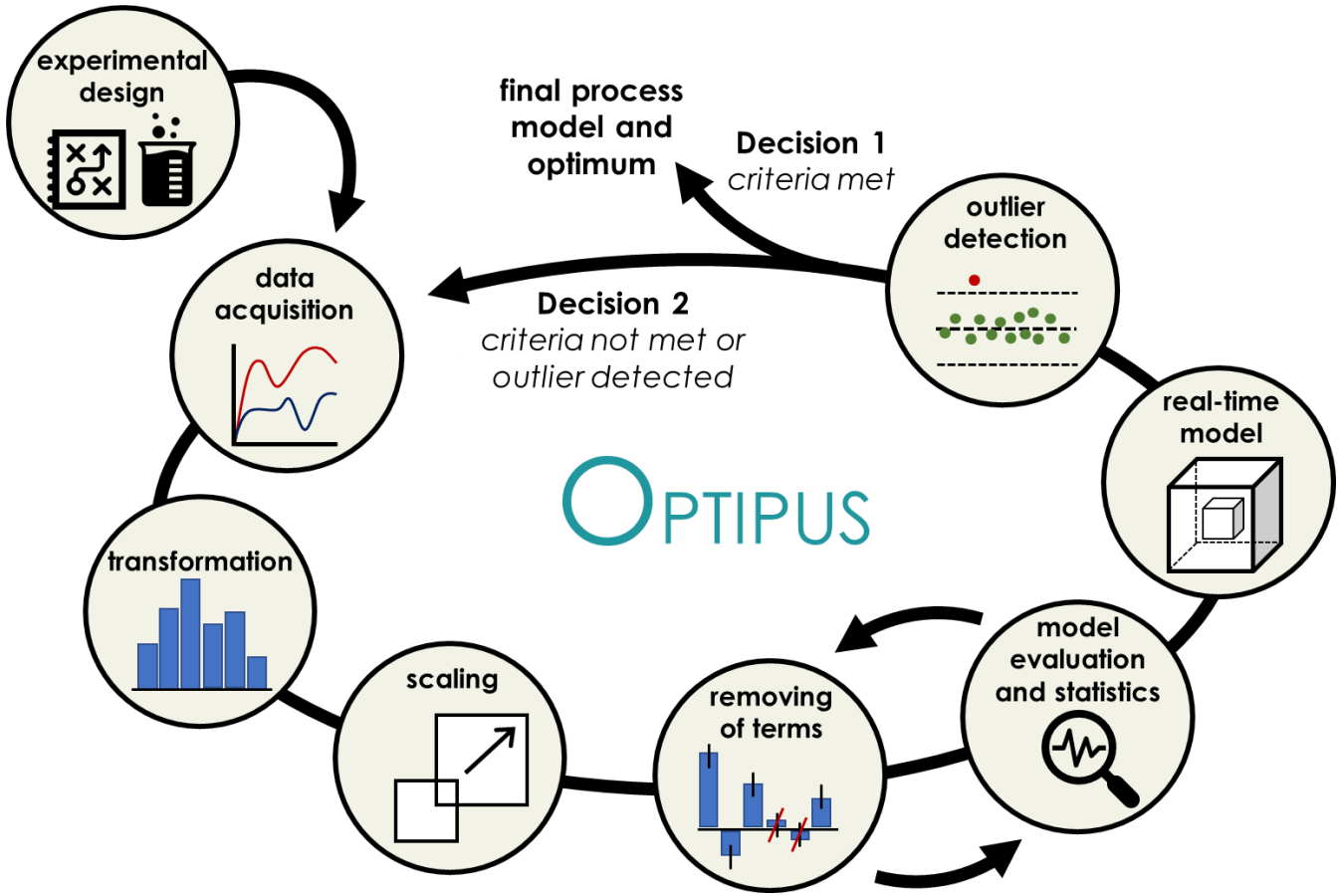


Knoll, S. et al. *React. Chem. Eng.* **2022**, *7*, 2375

Features of OPTIPUS

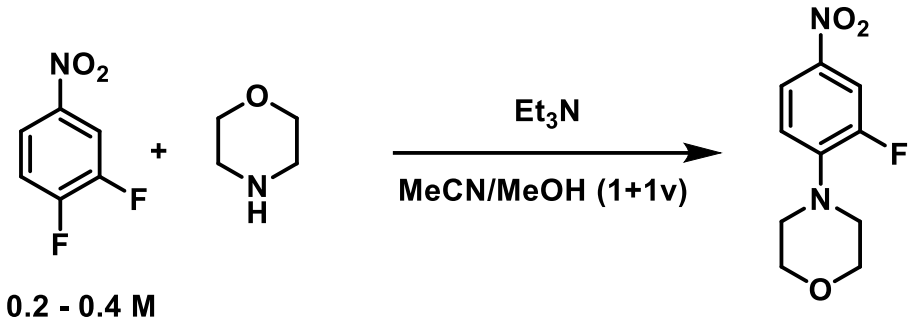
Sebastian Knoll

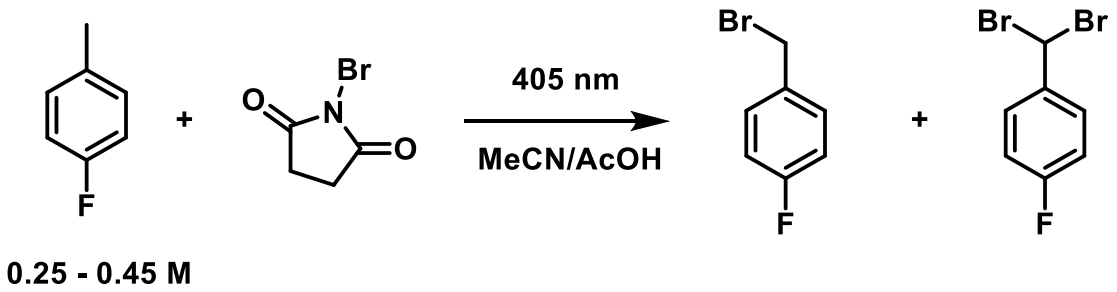
- **Python-based** program interacting with **XamControl**
  - Compatible with the current platform
- Performs consecutive DoE sets with increasing complexity
- Model evaluation after each set
- User experience
  - Graphical user interface
  - Real-time model visualization



Knoll, S. et al. *React. Chem. Eng.* **2022**, *7*, 2375

Case Studies





1. Nucleophilic Aromatic Substitution

- Using a S_NAr reaction to test system
- **4 variables**
  - Temperature
  - Concentration
  - Reagent ratio
  - Residence time

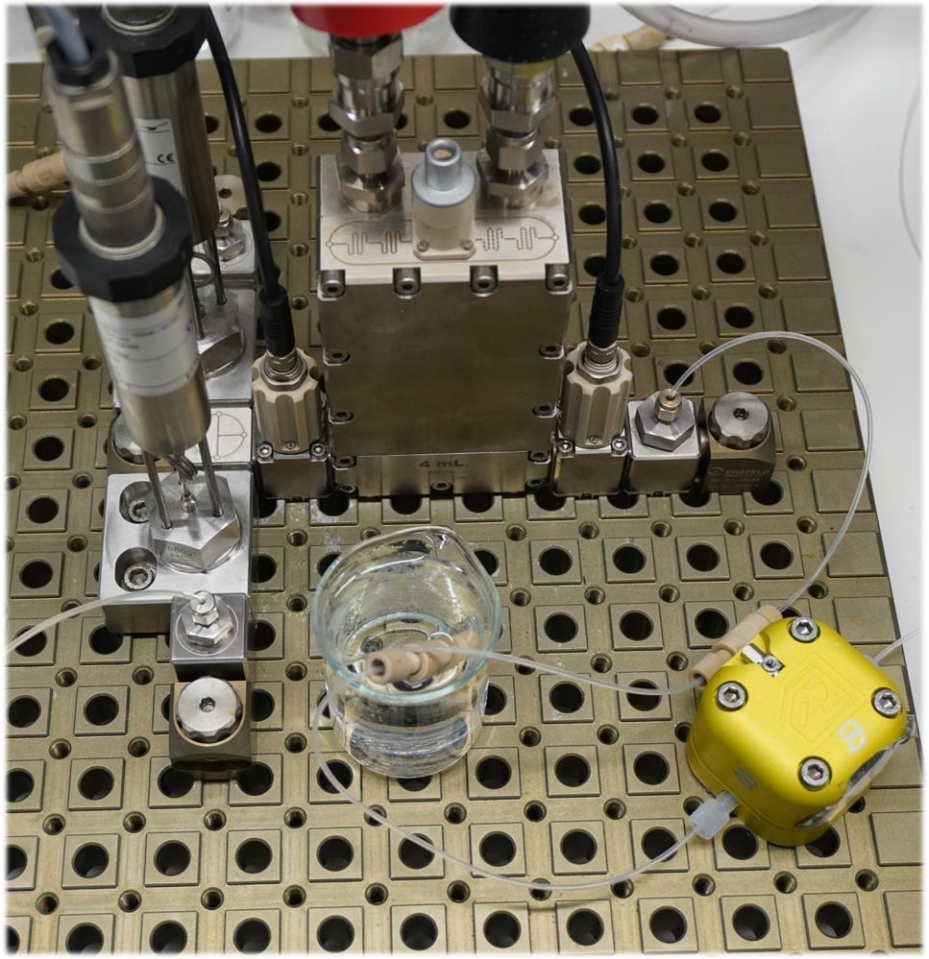
2. Photoinduced Benzylic Bromination

- "New" interesting variable: **light**
- 6 variables
  - T, c, reagent ratio, t_{res}
  - **Additive ratio**
  - **Light intensity**

Case Study 1: S_NAr

Workflow I

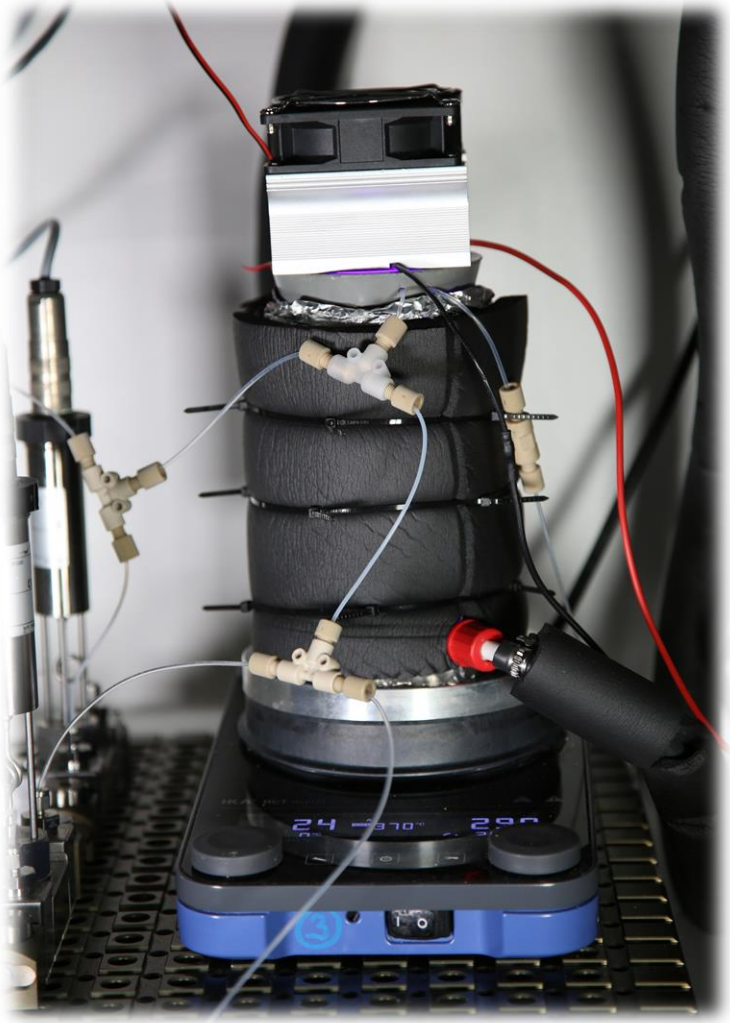
1. Automated DoE in broad design space
2. Automated DoE in narrow design space around **optimal point** (robustness)



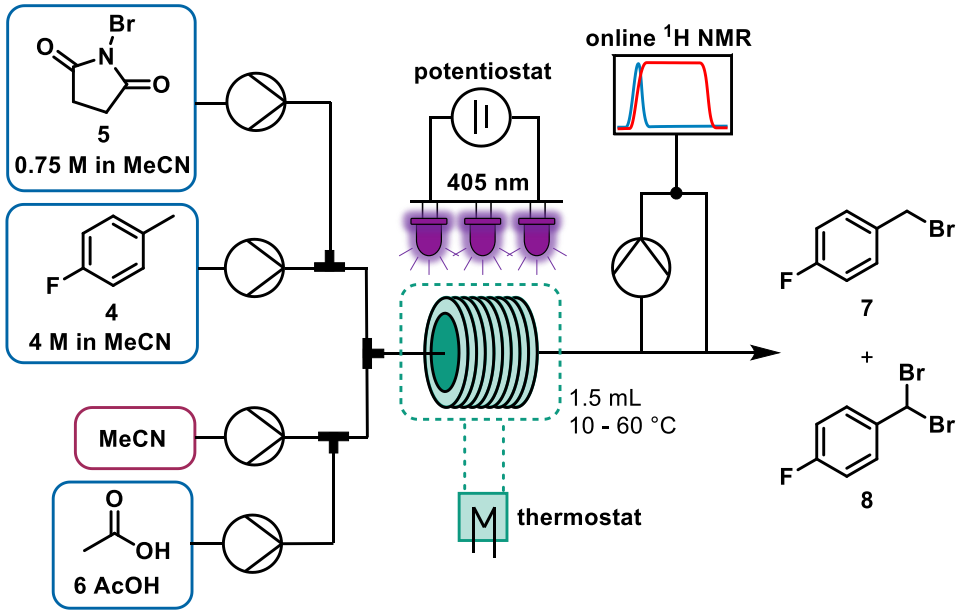
Case Study 2: Benzylic Bromination

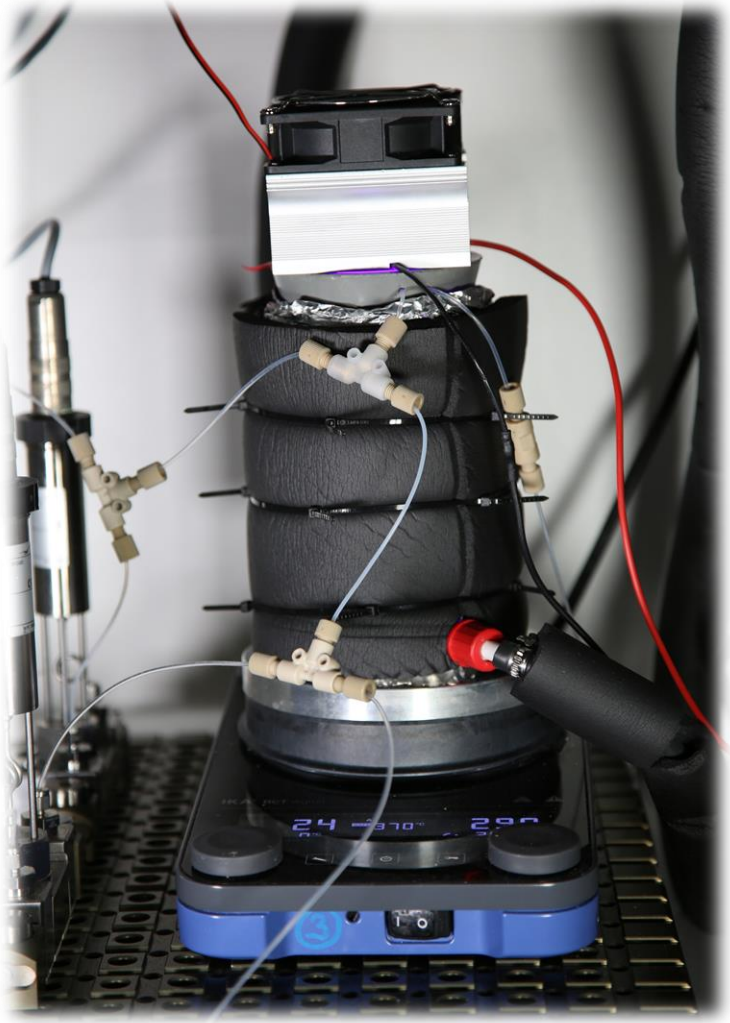
Workflow II

1. Self-Optimization with broad design space (TSEMO)
2. Automated DoE in optimum region

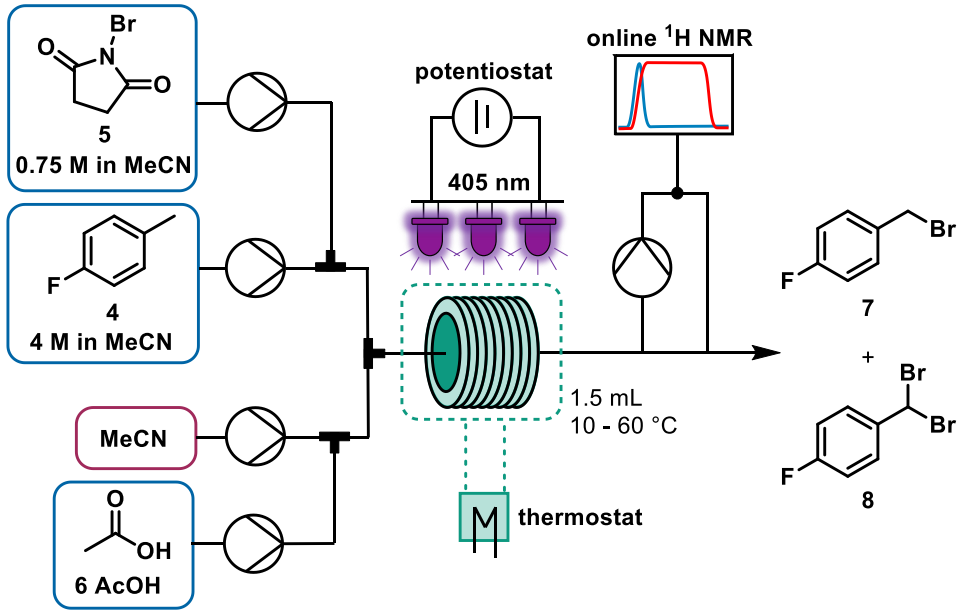


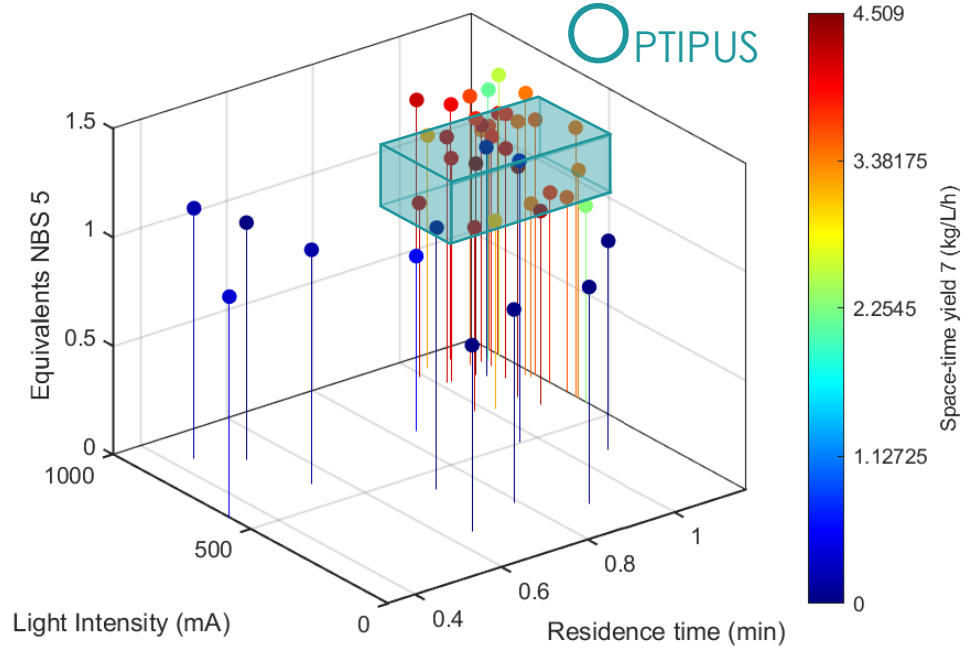
Case Study 2: Benzylic Bromination





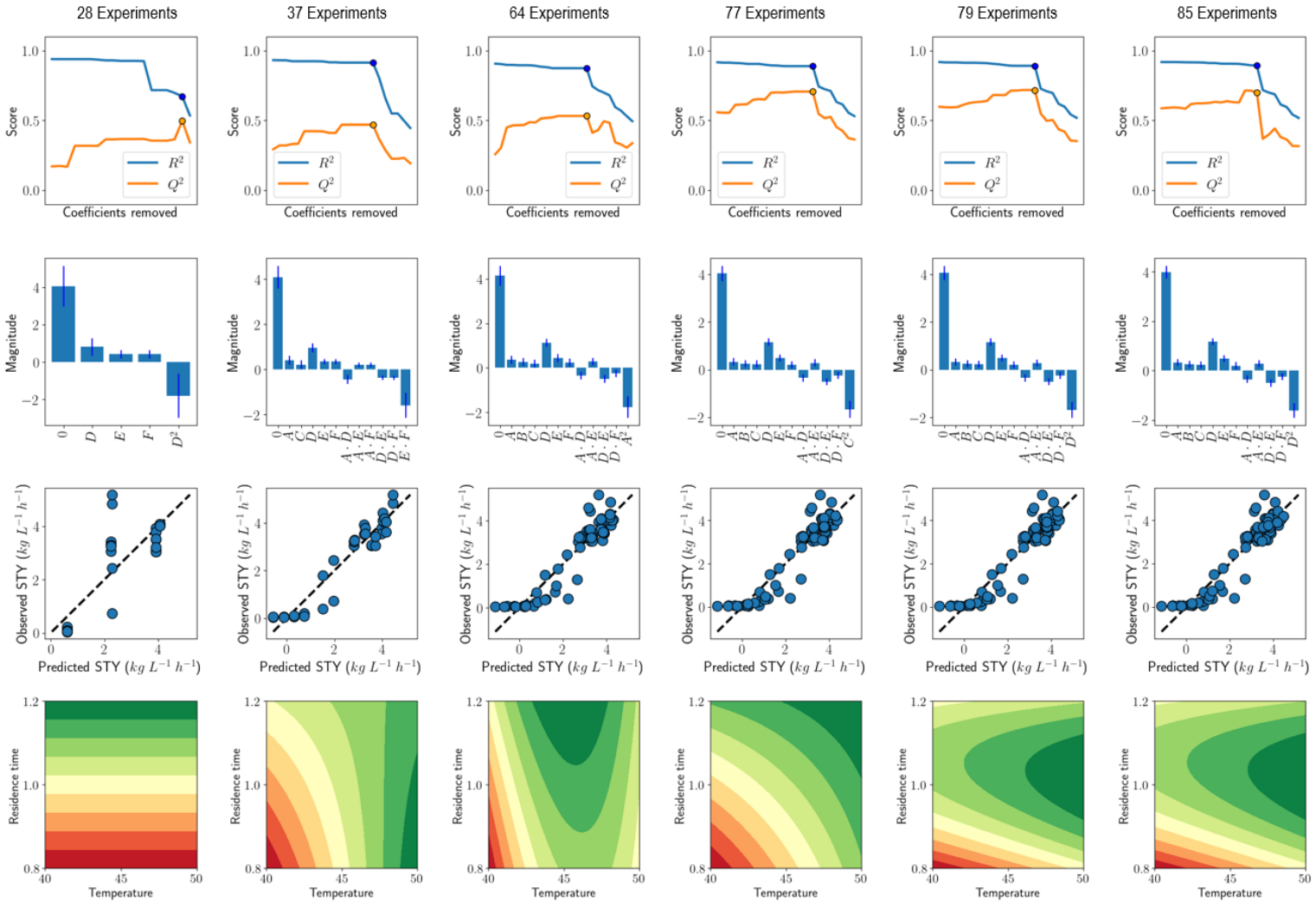
Case Study 2: Benzylic Bromination





	equiv **5**	temp (°C)	conc **4** (M)	light int. (mA)	t_{res} (min)	equiv **6**
TS-EMO	0.8 – 1.3	20 – 60	0.25 – 0.45	100 – 950	0.3 – 1.2	0.00 – 0.1
OPTIPUS	0.9 – 1.1	40 – 50	0.40 – 0.45	750 – 950	0.8 – 1.2	0.01 – 0.05

Case Study 2: Benzylic Bromination



Acknowledgements

C. Oliver Kappe
Clemens Jusner, Florian Ort, Rene Lebl, Chris Hone, David Cantillo, Klara Silber, Christine Schiller, Peter Weiss (RCPE and Uni Graz)

Peter Sagmeister

Stephan Sacher, Jakob Rehrl, Julia Kruisz, Selma Celikovic (RCPE)

Frederic Buono, Dominique Hebrault, Thomas Tampone (Boehringer Ingelheim USA)

Martin Sipek, Dirk Kirschneck (Evon & Microinnova)

Sebastian Knoll, Ismael Castillo, Martin Horn (IRT, TU Graz)

Boehringer Ingelheim

GOFLOW

TU Graz

UNI GRAZ

JOANNEUM RESEARCH

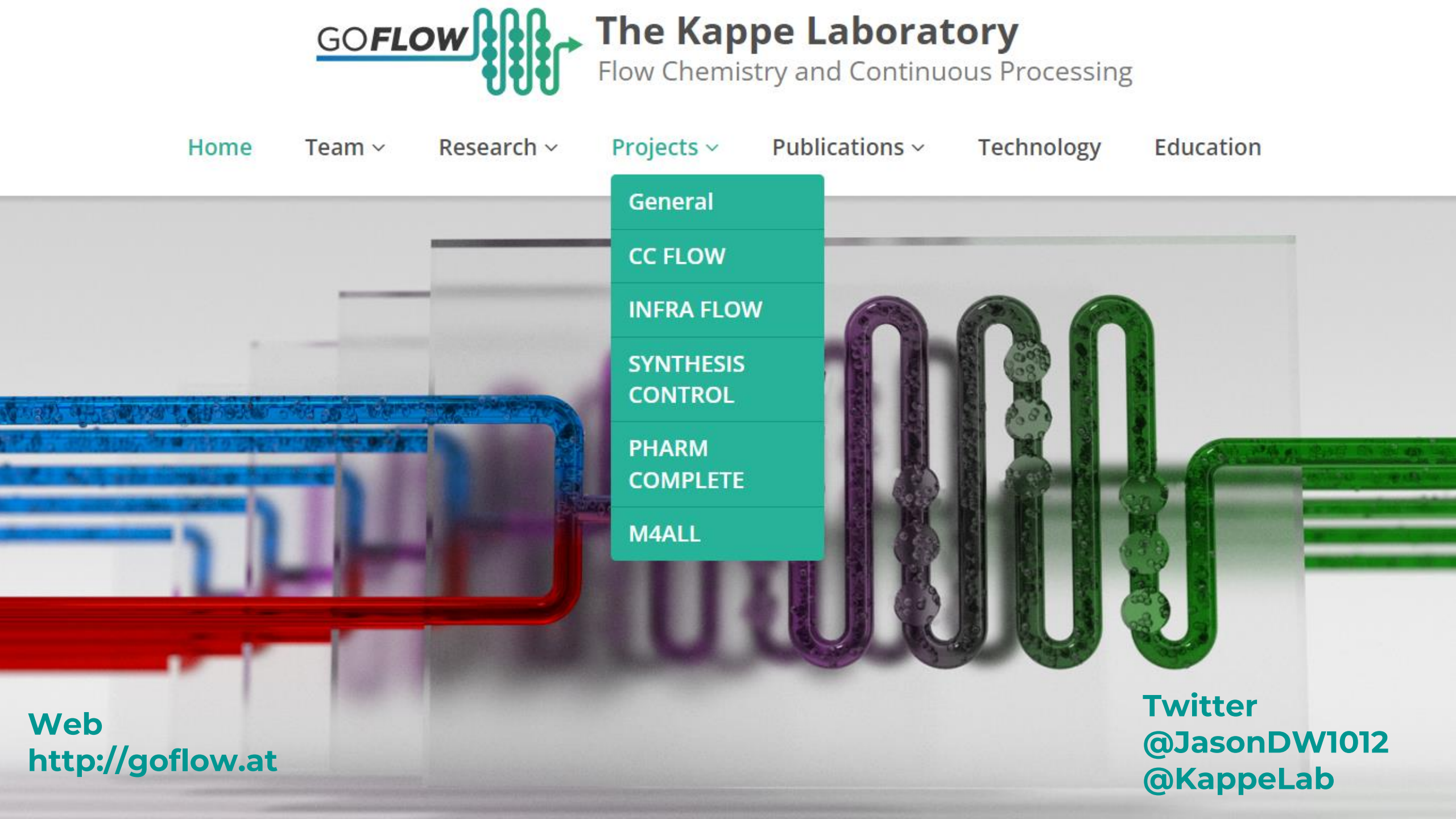
Federal Ministry Republic of Austria Climate Action, Environment, Energy, Mobility, Innovation and Technology

Federal Ministry Republic of Austria Labour and Economy

FFG Promoting Innovation.

Das Land Steiermark Wirtschaft, Tourismus, Regionen, Wissenschaft und Forschung

SFG NEUES DENKEN. NEUES FÖRDERN.


GOFLOW
The Kappe Laboratory
Flow Chemistry and Continuous Processing
Home
Team
Research
Projects
Publications
Technology
Education
General
CC FLOW
INFRA FLOW
SYNTHESIS CONTROL
PHARM COMPLETE
M4ALL
Web
http://goflow.at
Twitter
@JasonDW1012
@KappeLab

Disclaimer