Automation of Pharmaceutical Production

Stephan Sacher[1], Jakob Rehrl[1], Peter Sagmeister[1,2], Jason D. Williams[1,2], Ismael Castillo[3], Selma Celikovic[1,3], Martin Sipek[4], C. Oliver Kappe[1,2], Martin Horn[3], Johannes Khinast[1,5]

1 Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13/2, 8010 Graz, Austria
2 Institute of Chemistry, University of Graz, Heinrichstraße 28, 8010 Graz Austria
3 Institute of Automation and Control, Graz University of Technology, Inffeldgasse 21/B/I, 8010 Graz Austria
4 evon GmbH, Wollsdorf 154, 8181 St. Ruprecht an der Raab, Austria
5 Institute for Process and Particle Engineering, Graz University of Technology, Inffeldgasse 13/3, 8010 Graz Austria

Evon up 2 date, 22.6.2022

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

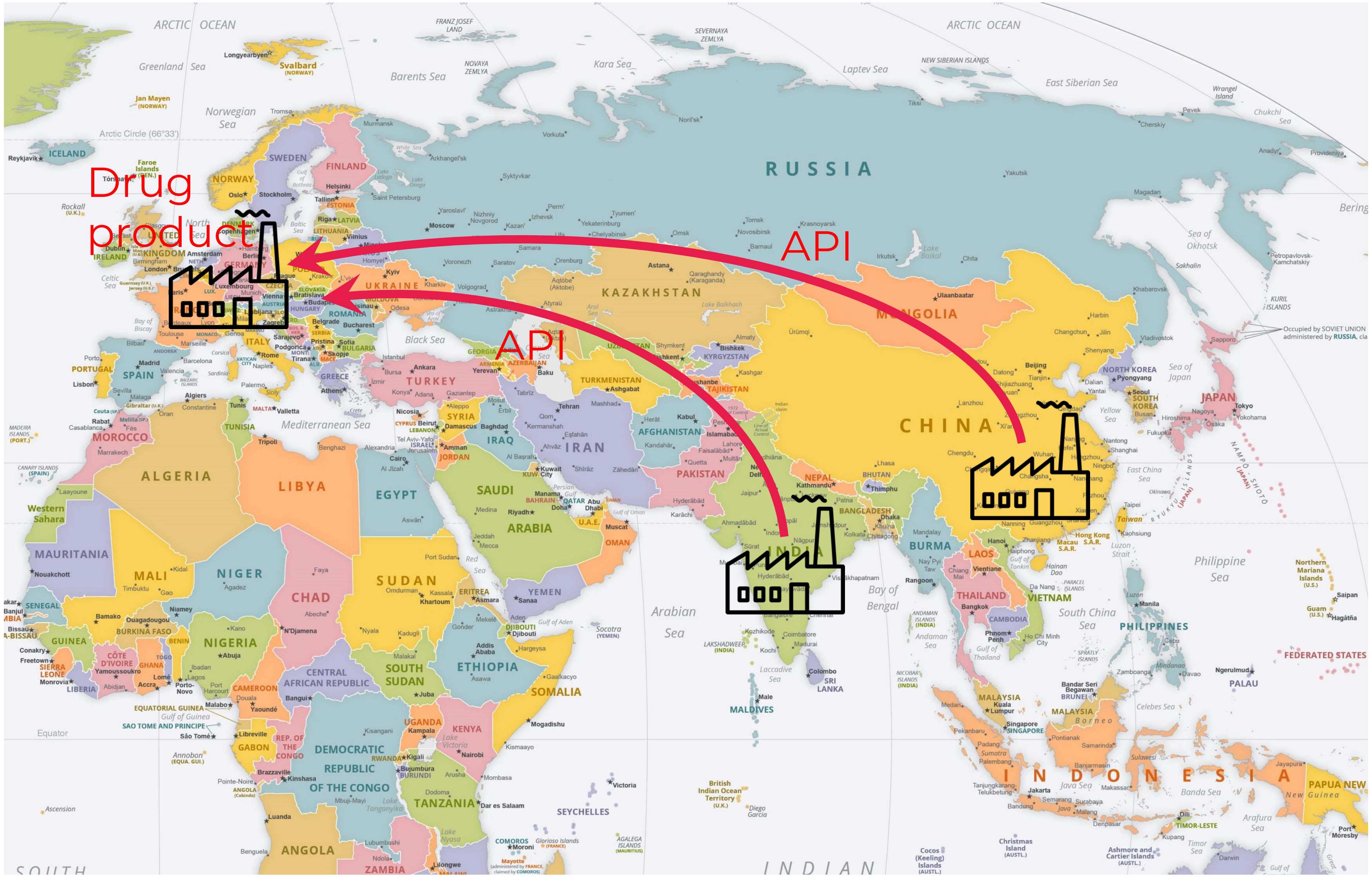
Federal Ministry Republic of Austria Digital and Economic Affairs

FFG Promoting Innovation.

Das Land Steiermark

SFG NEUES DENKEN. NEUES FÖRDERN.

Pharmaceutical Manufacturing Chain



http://karteplan.com/eurasien/eurasien-politische-karte.jpg

Process Concepts

Conventional batch processing

Low flexibility

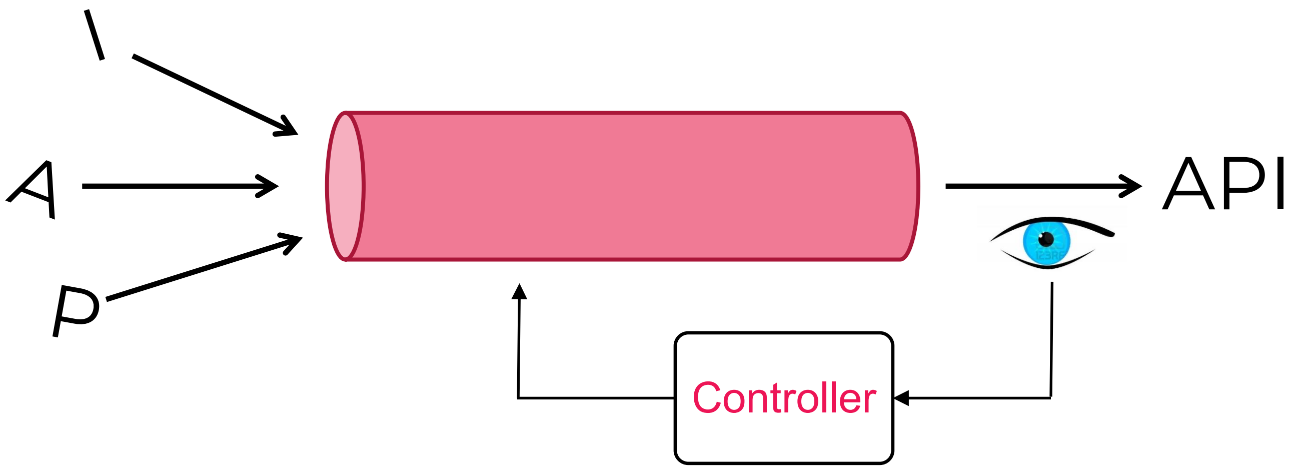
No real-time feedback

Waste

Quality variation

Batch loss, if OOS

Continuous processing with closed loop control



Real-time feedback & control actions

High flexibility

Less waste

Robust quality

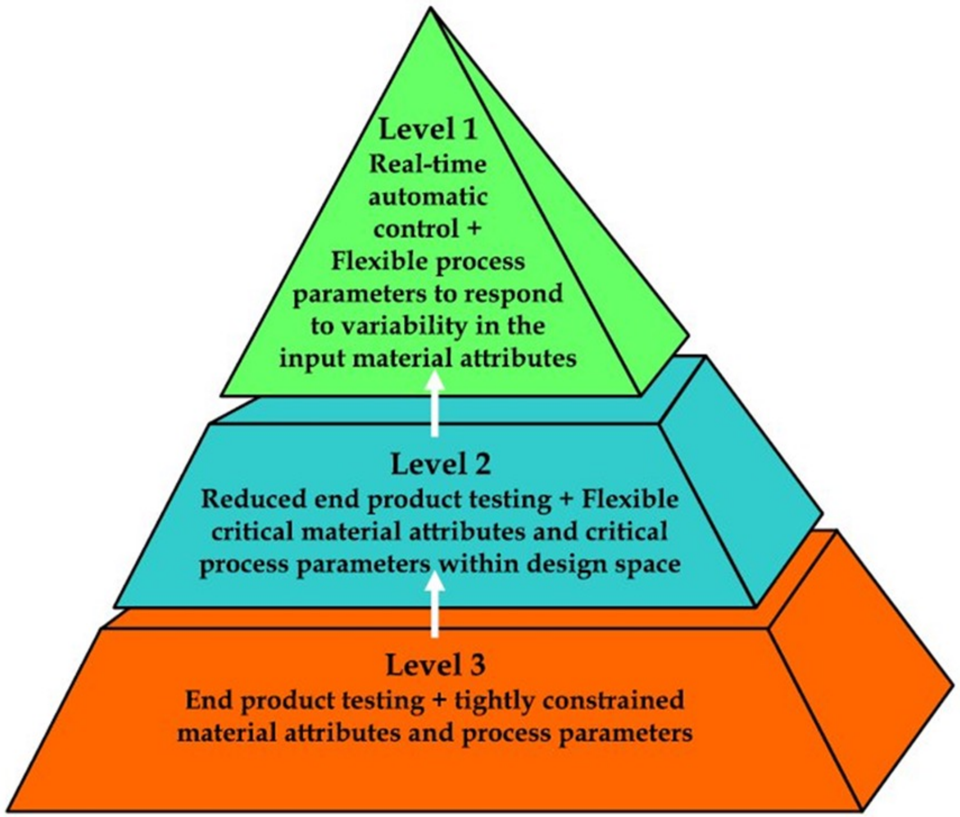
Easy scale-up

Strategy to Achieve an Automated Process

- Control concept supporting a fully automated continuous manufacturing process (Level 1)
- Optimized start-up and steady state operation
- Real-time control actions and quality control
- Mitigation of OOS events
- Control of mass flow rates through all unit operations
- Control of quality attributes of intermediates and product

Quality by Control (QbC)

1. Risk-based PAT strategy
2. Development of process models
3. Development of a hierarchical control strategy
4. Implementation of closed loop control

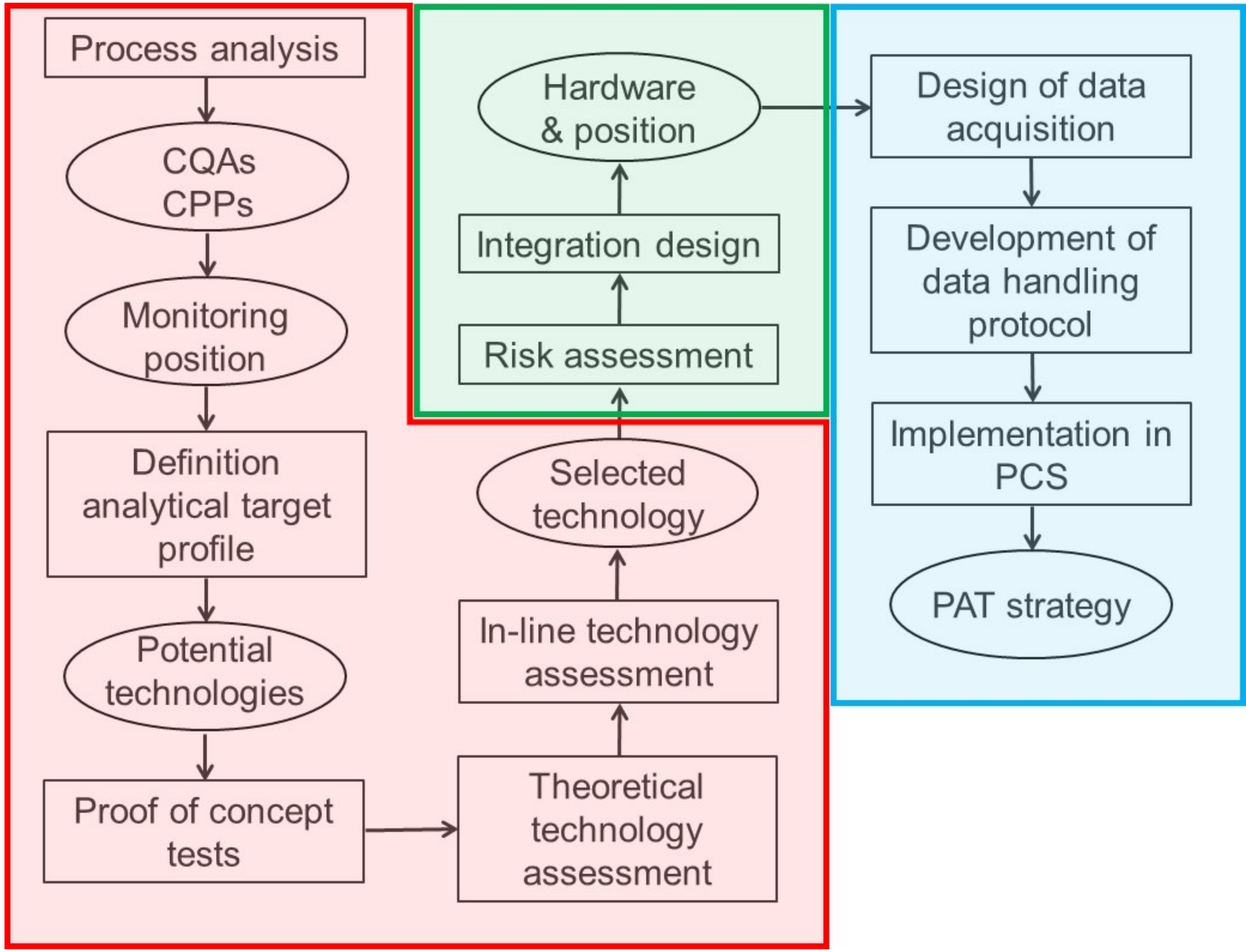


Published by FDA: Lawrence Yu et al., AAPS Journal 2014, 16, 4, 771-783

Utilization of PAT

- Generation of information on process and material state from process data in real-time is essential
- This requests
  - PAT concept over the full process chain
  - Proper in-line monitoring technology (accuracy, resolution, acquisition rate, reproducibility, etc.) for each CQA relevant for the control concept
  - Knowledge to develop the right information out of a huge amount of data
  - Interaction of PAT with process control system (PCS)

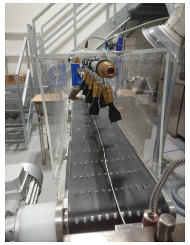
PAT implementation workflow



S. Sacher et. al. 2022, PAT implementation for advanced process control in solid dosage manufacturing – a practical guide. Int. J. Pharm. https://doi.org/10.1016 j.ijpharm.2021.121408

Process Digitalization

Process equipment & sensors

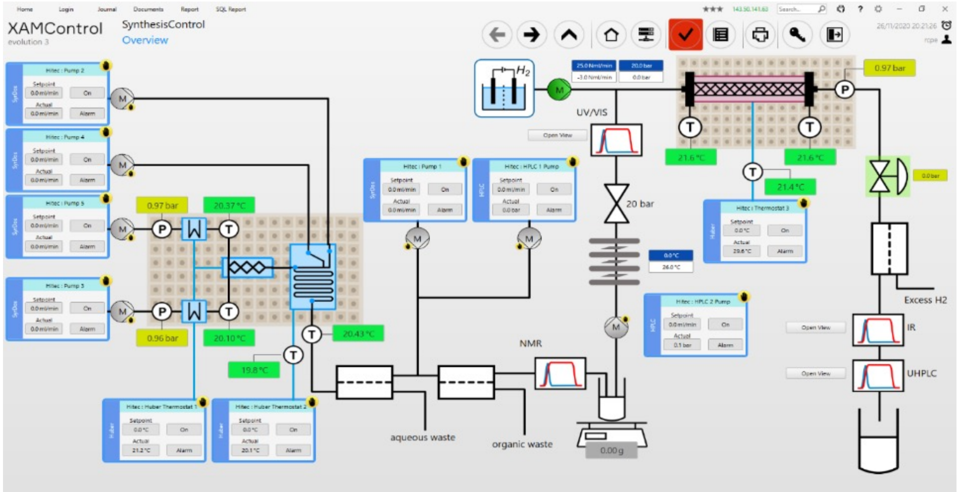


Interfaces

Process data →

← Actuating signals

Digital twin & human machine interface



Process models

$$r_1 = k_{0,1} e^{-\frac{E_{a,1}}{RT}} c_{3N-ClBA}^{o_{1,1}} c_{NaOH}^{o_{2,1}} \qquad \frac{dc_{3-NSA}}{dt} = r_1$$

$$r_2 = k_{0,2} e^{-\frac{E_{a,2}}{RT}} c_{5N-ClBA}^{o_{1,2}} c_{NaOH}^{o_{2,2}} \qquad \frac{dc_{3N-ClBA}}{dt} = -r_1$$

$$\frac{dc_{NaOH}}{dt} = -2r_1 - 2r_2 \qquad \frac{dc_{5-NSA}}{dt} = r_2 \qquad \frac{dc_{5N-ClBA}}{dt} = -r_2$$

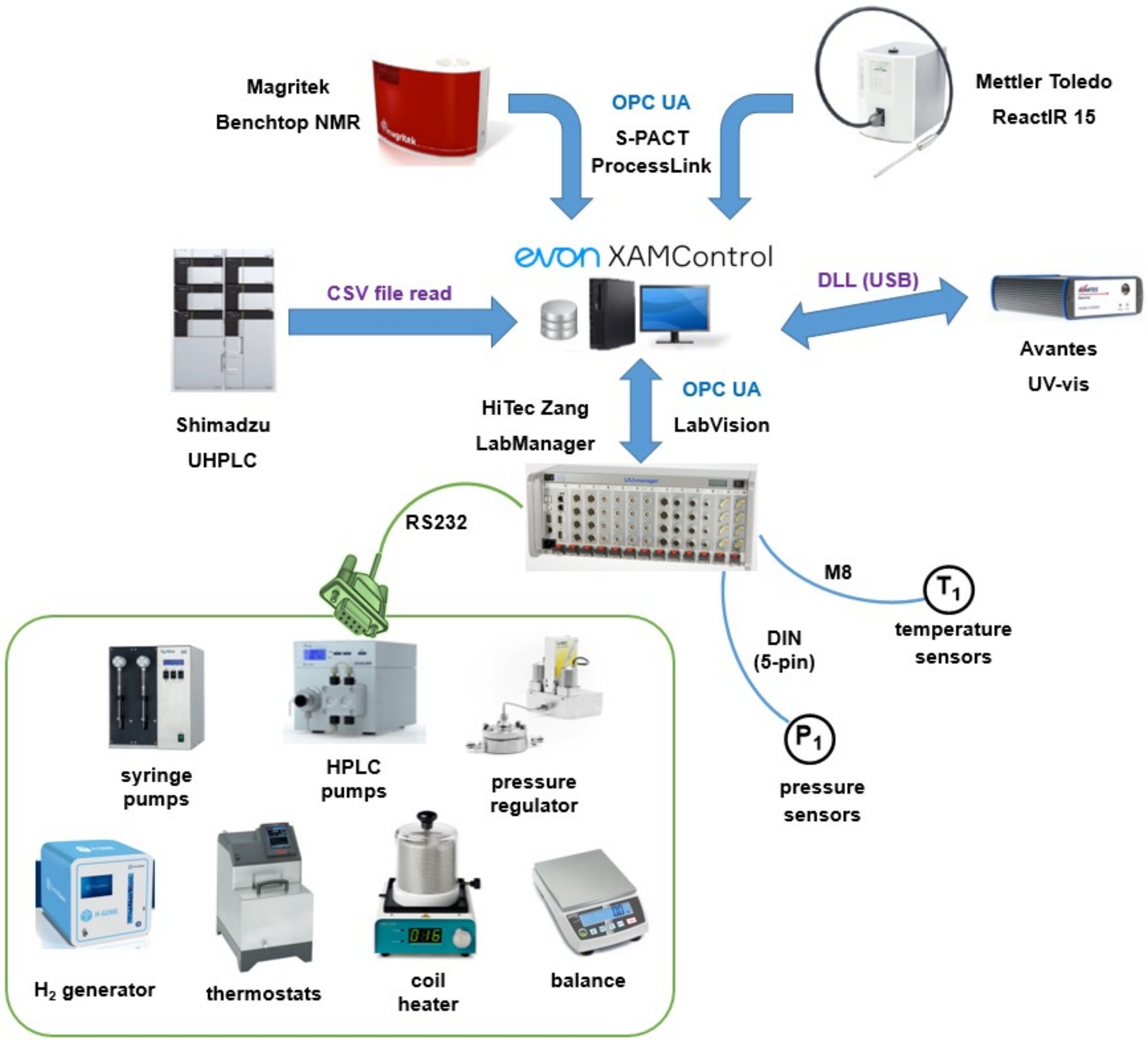
$$\frac{\partial c(t,l)}{\partial t} = -\frac{v_0 \partial c(t,l)}{\partial l} + \text{"reaction rates"}$$

Optimal control

$$\min \sum_{i=1}^{np} \boldsymbol{e}_{k+i}^T \boldsymbol{Q} \boldsymbol{e}_{k+i} + \sum_{i=0}^{nc} \boldsymbol{u}_{k+i}^T \boldsymbol{R} \boldsymbol{u}_{k+i}$$

subject to:
input constraints $\boldsymbol{u}_{\min} \leq \boldsymbol{u}_k \leq \boldsymbol{u}_{\max}$
output constraints $\boldsymbol{y}_{\min} \leq \boldsymbol{y}_k \leq \boldsymbol{y}_{\max}$
process model

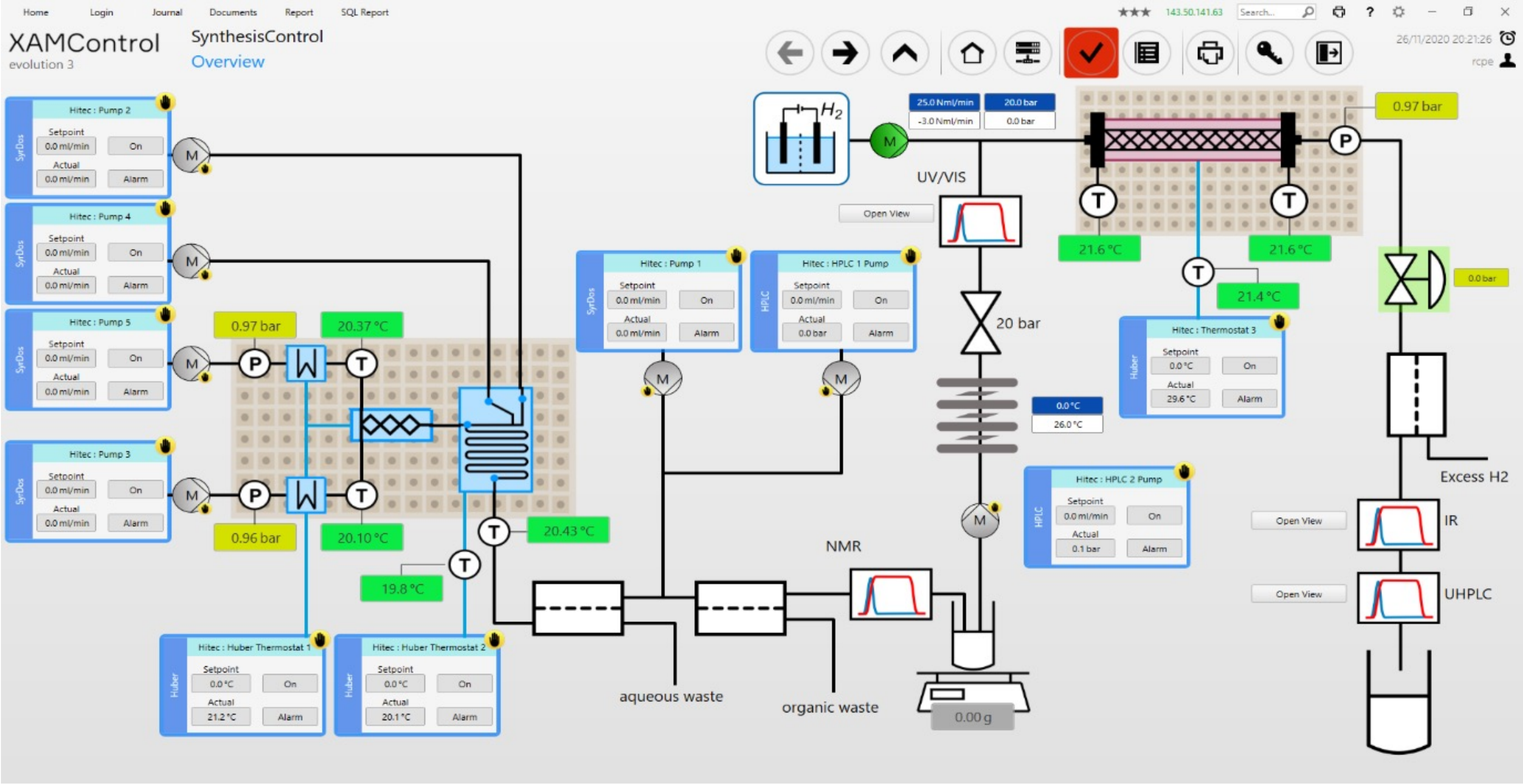
Data Acquisition Architecture



- Interfaces with multivariate sensors via OPC UA (NMR and IR), net DLL (UV/Vis) and csv file transfer (UHPLC)
- Process equipment connected via various interfaces and HiTec LabManager
- Data alignment and process control in XAMControl
- Implementation of control concept in XAMControl after optimization in simulation

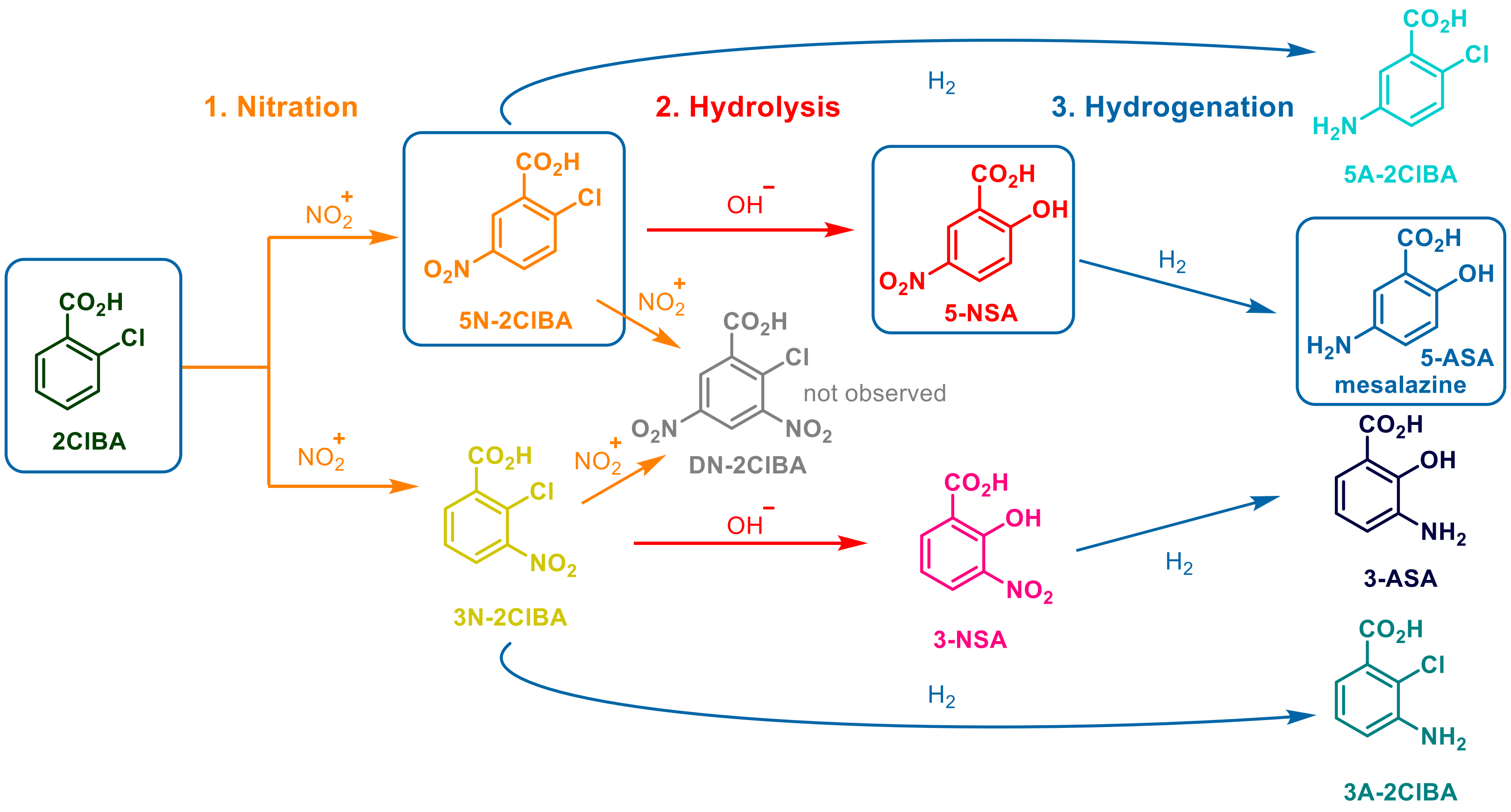
P. Sagmeister et al. (2021), Advanced Real-Time Process Analytics for Multistep Synthesis in Continuous Flow, Angewandte Chemie Int. Ed. https://doi.org/10.1002/anie.202016007

Process Automation



- XAMControl as process control system (PCS)
- Execution of control concept via SCADA and PLCs
- Execution of process models and chemometric models in the PCS
- Execution of PAT methods
- Human machine interface (HMI)
- Process visualization
- Material tracking
- Recipe management
- Storage of relevant process data
- Remote control function

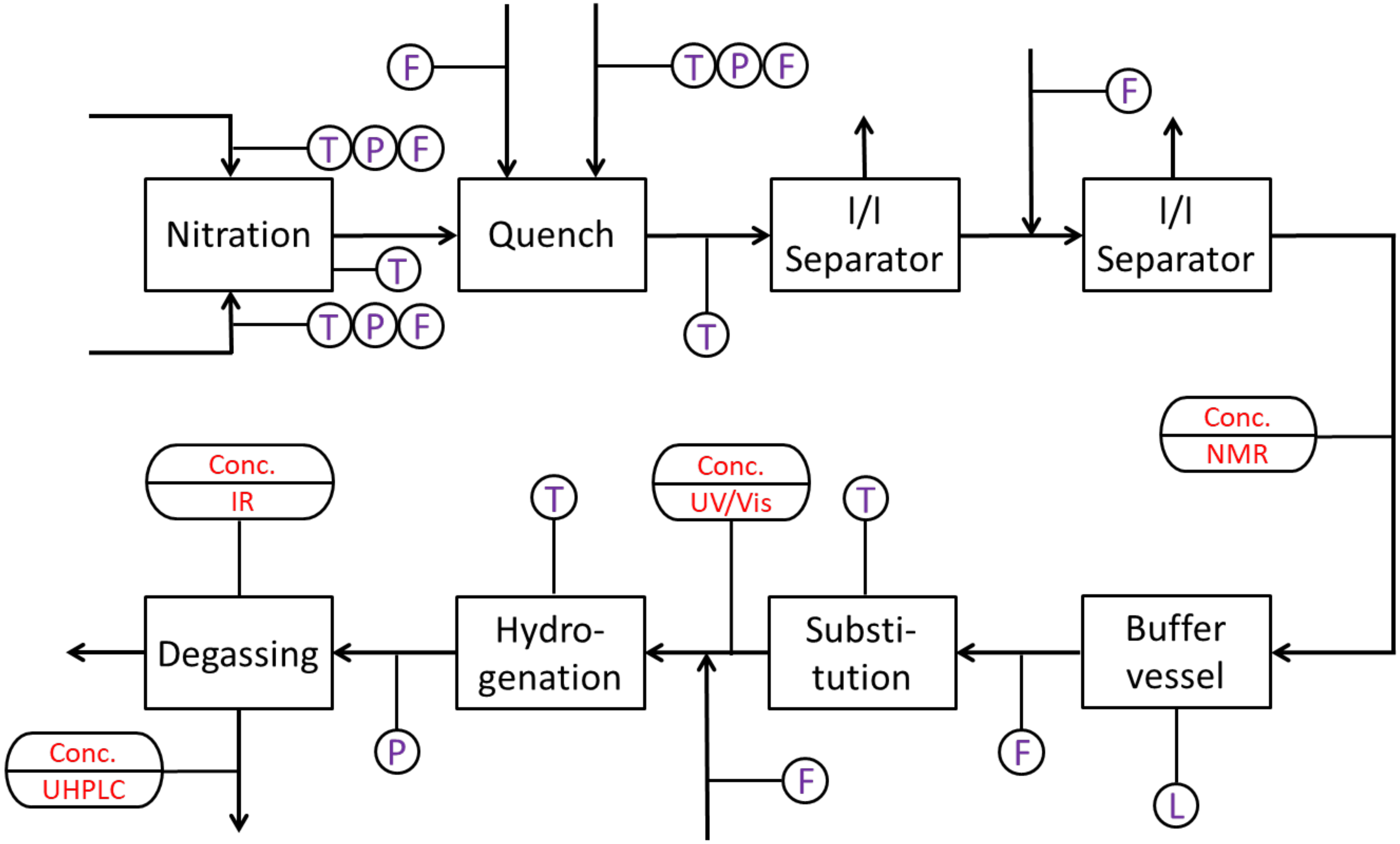
API Synthesis



- Synthesis of mesalazine (5-aminosalicylic acid, 5-ASA) as target API
- Substrate: 2-chlorobenzoic acid (2ClBA)
- 3 reaction steps
  - Nitration with nitric acid
  - Hydrolysis/aromatic substitution
  - Hydrogenation
- Intermediates: 5N-2ClBA, 5-NSA
- Side products: 3N-2ClBA, 3-NSA, 3-ASA, 3A-2ClBA, 5A-2ClBA

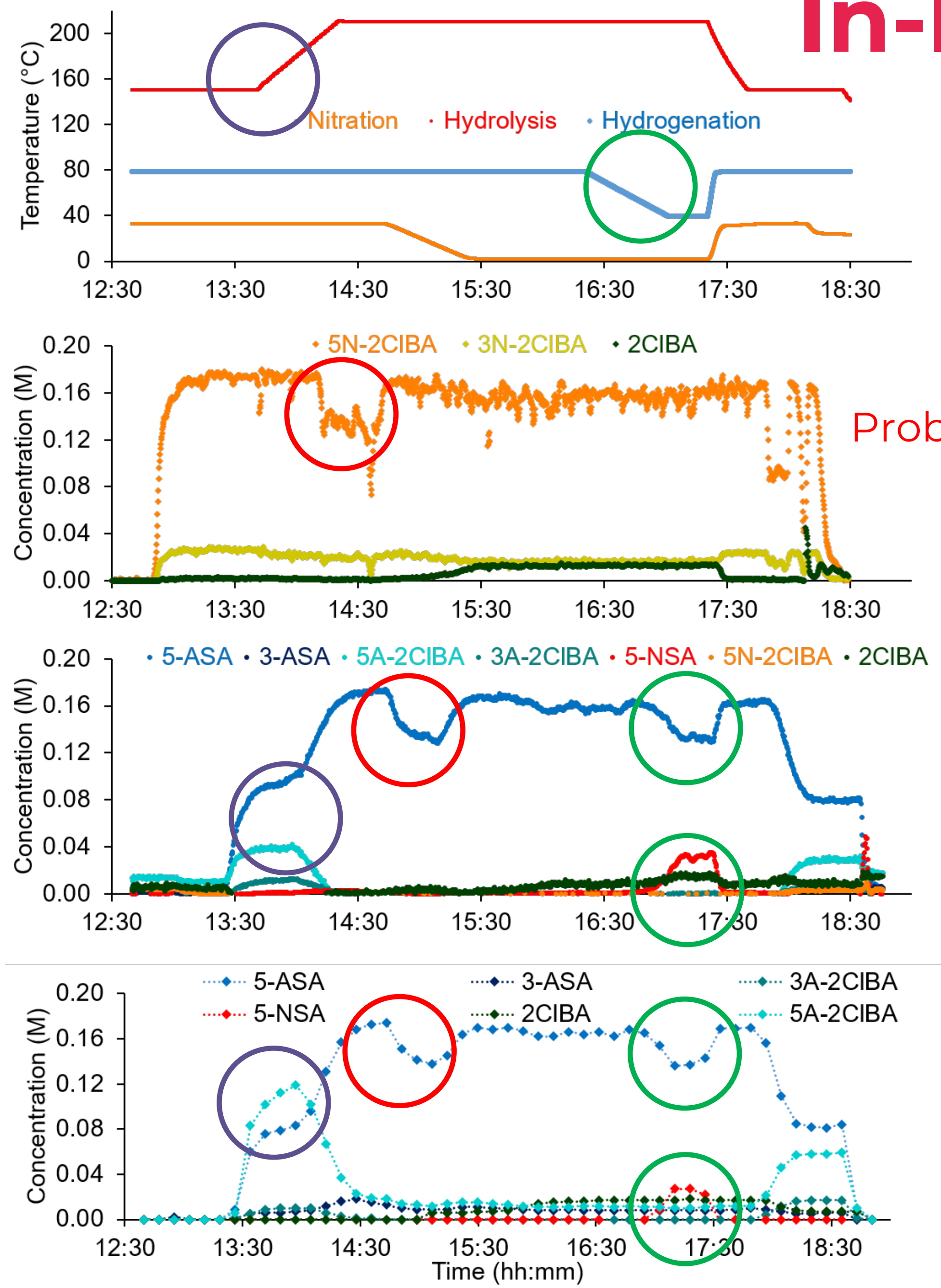
P. Sagmeister et al. (2021), Advanced Real-Time Process Analytics for Multistep Synthesis in Continuous Flow, Angewandte Chemie Int. Ed. https://doi.org/10.1002/anie.202016007

PAT Concept for API Synthesis



- In-line monitoring of concentration (yield, impurities) after each reaction step
- Prediction via hard modeling (NMR), PLS (IR) and neural network (UV/Vis)
- UHPLC at process end for exact concentration measurement
- Acquisition rates of 12s (NMR), 2s (UV/Vis), 15s (IR), 7.5min (UHPLC)
- In-line measurement of temperature, pressure via univariate sensors and flow rate from equipment data

In-line Monitoring



Temperature profile

Problem in l/l-separation

NMR

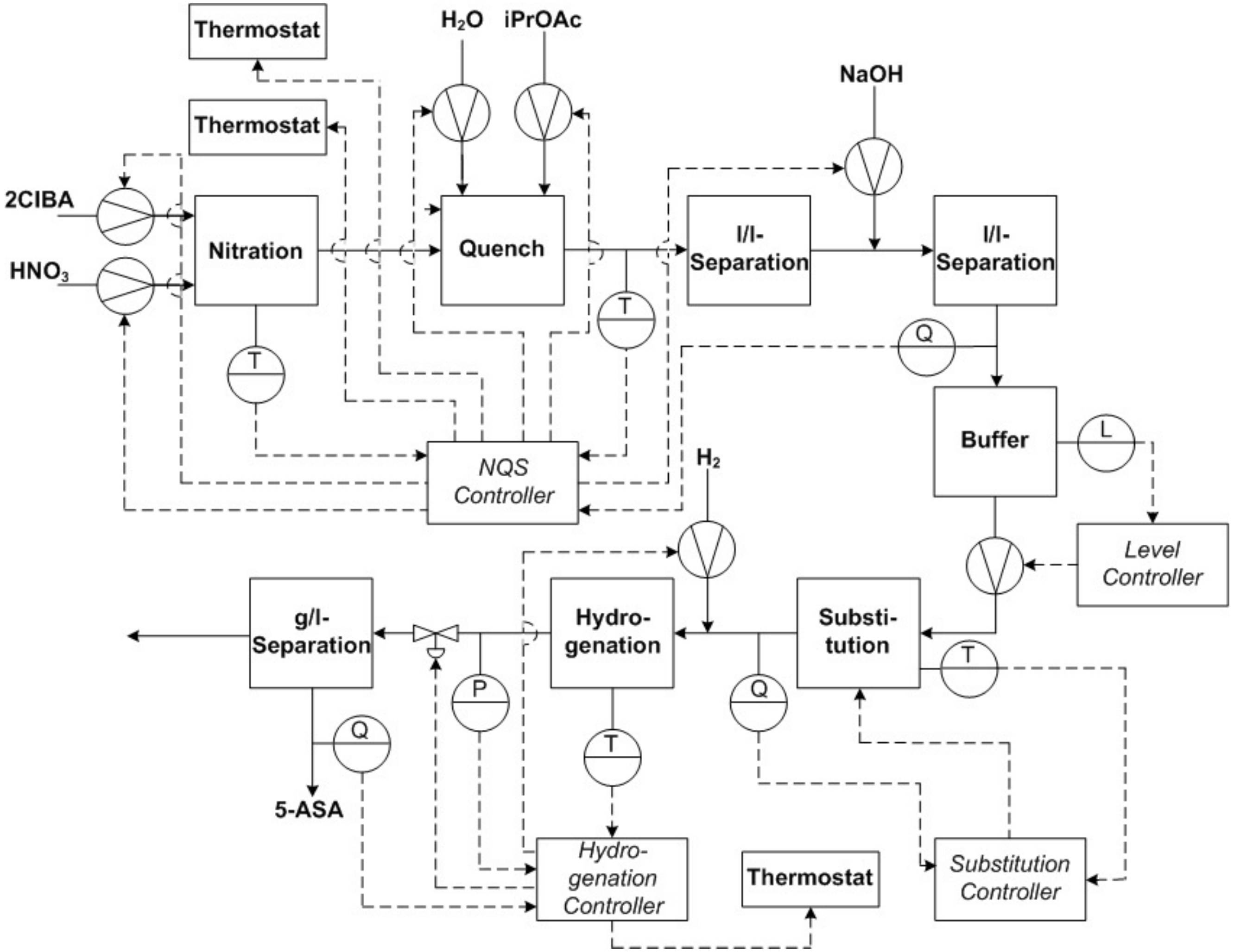
IR

UHPLC

- In-line monitoring of concentration (yield, impurities) after each reaction step
- Temperature changes lead to changes in conversion and selectivity
- Low initial substitution (hydrolysis) temperature leads to low 5-ASA output and high 5A-2ClBA
- Problem in separation leads to decrease in intermediate and product
- Temperature decrease in hydrogenation leads to drop in product (5-ASA) and more unconverted 5-NSA
- Process events can be clearly monitored and detected

P. Sagmeister et al. (2021), Advanced Real-Time Process Analytics for Multistep Synthesis in Continuous Flow, Angewandte Chemie Int. Ed. https://doi.org/10.1002/anie.202016007

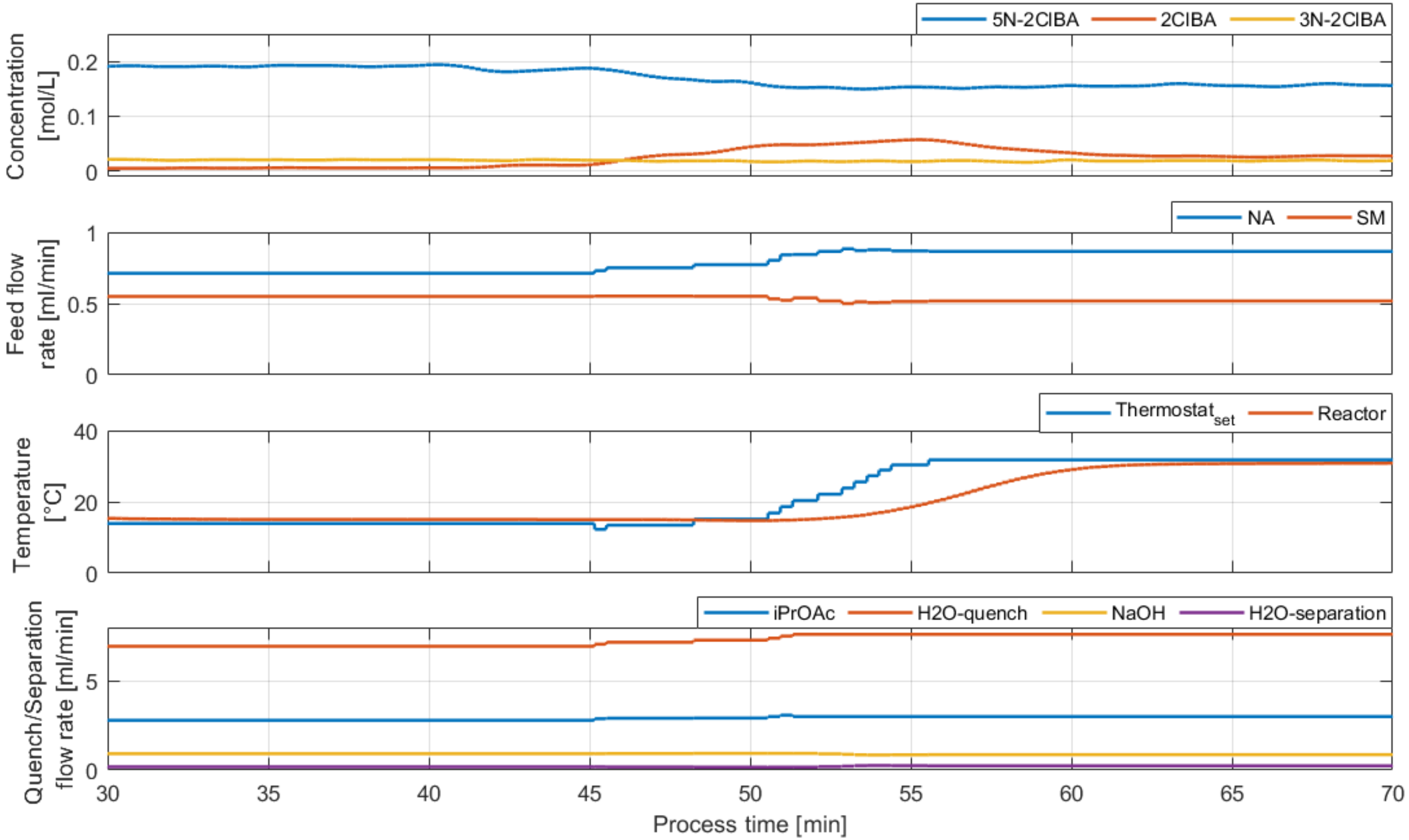
Model-based Control Concept



Sacher, S. et al., 2022. Automated and continuous synthesis of drug substances. Chem. Eng. Res. Des. 177, 493-501. doi: 10.1016/j.cherd.2021.10.034.

- Real-time information on process (PPs) and material state (QAs) to trigger control actions
- Model-predictive control (MPC) concept, PID for buffer
- Independent control loops allow for flexibility (objectives and constraints)
- Main control objective
  - Maximize throughput and yield
  - Minimize impurities (raw and side products)
- Constraints for all manipulated variables and rate changes according to process, equipment behavior, etc.

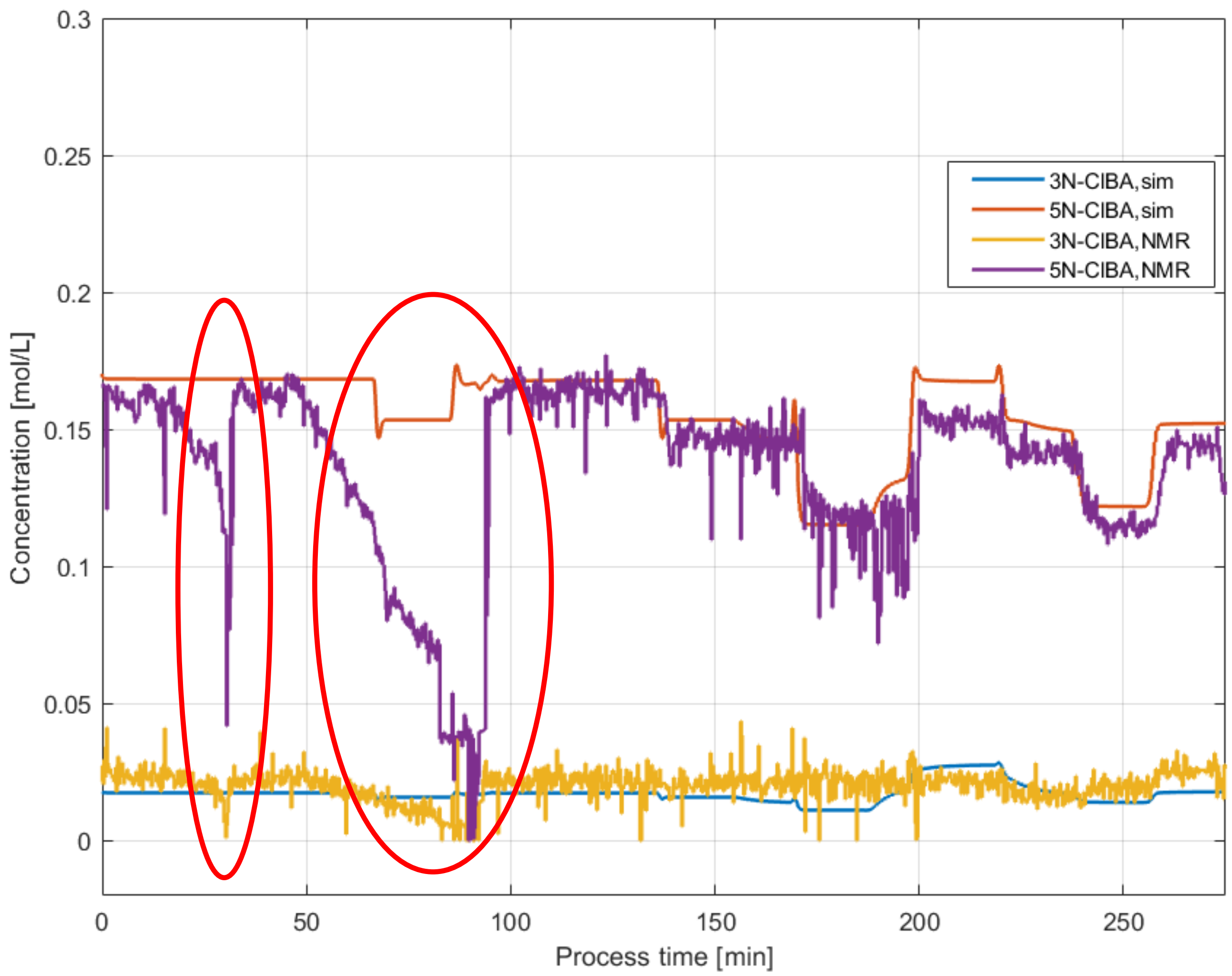
Automation of API Synthesis



S. Sacher et. al. 2021, Automated and continuous synthesis of drug substances. Chem. Eng. Res. Des. 177, 493-501. doi: 10.1016/j.cherd.2021.10.034.

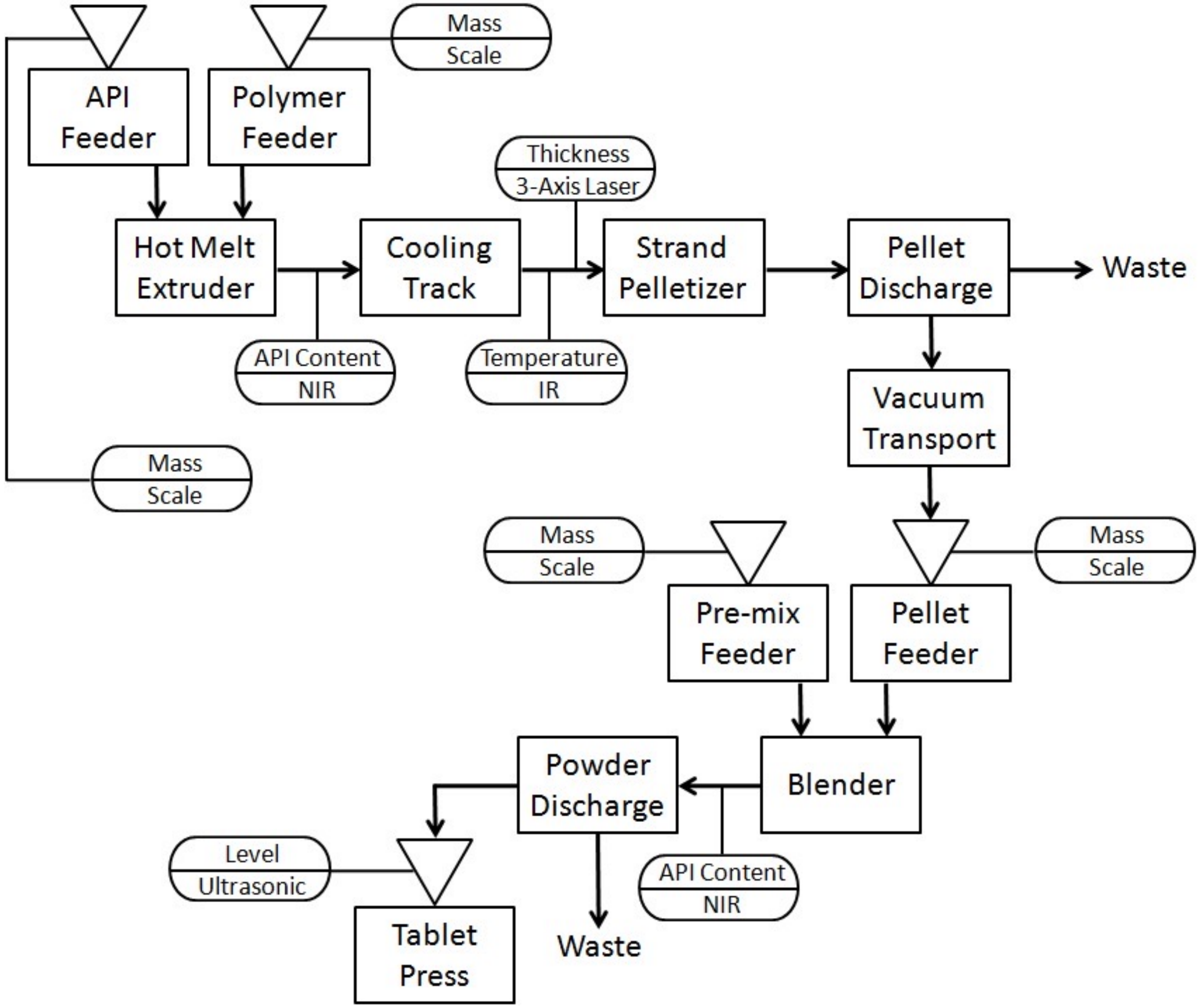
- Steady state operation of nitration
- At 40 min the feed stock of nitrating agent (NA) was exchanged to 50% nominal concentration
- Concentration of product (5N-2ClBA) starts to decrease and starting material (2ClBA) increases
- Controller reacts immediately and manipulates feed rates and reaction temperature
- New steady state is reached with optimized yield at 55 min

Automated Fault Detection



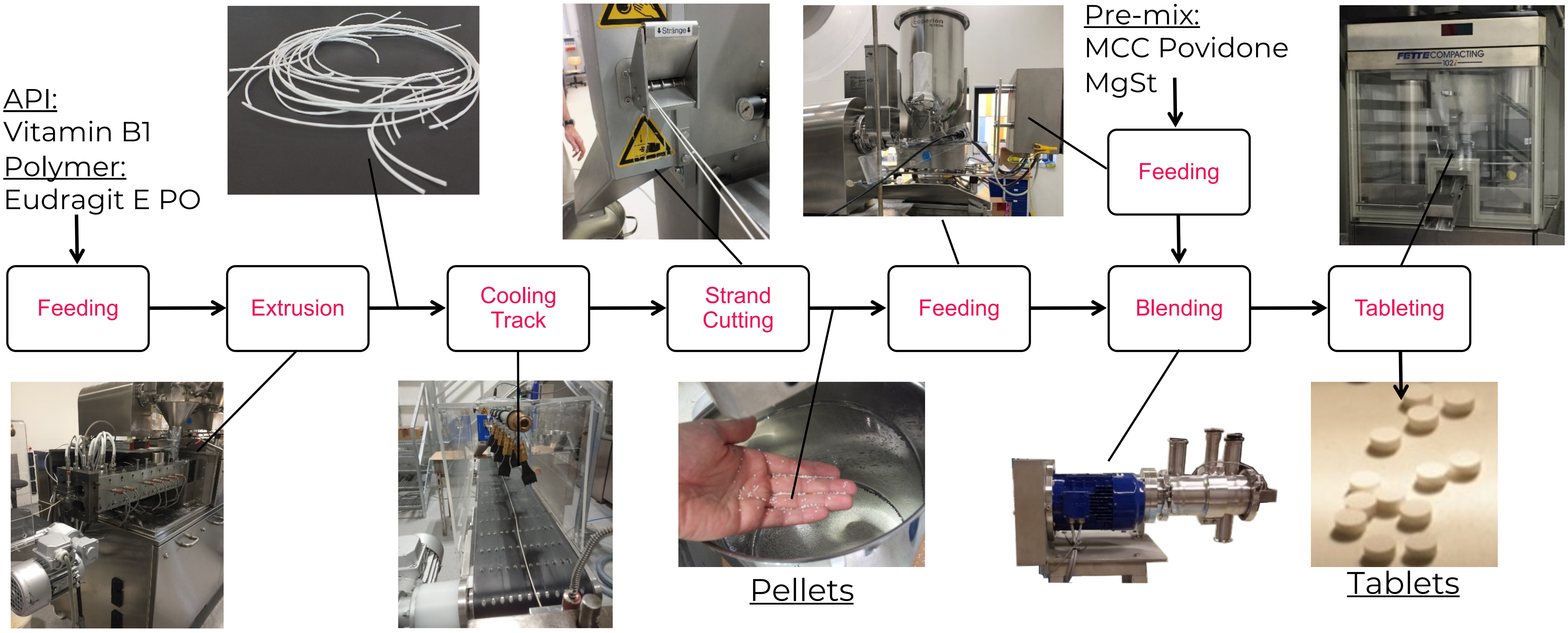
- Fault detection based on comparison between observer and measurement
- Concentration after nitration-quench-separation
- Deviation (marked in red) indicates process fault
- Concentration of product and side-product decreased due to issues with separation unit
- Product and side-product were diverted to waste
- Due to real time fault detection the problem could be recognized and solved

Tableting via Extrusion and Direct Compaction



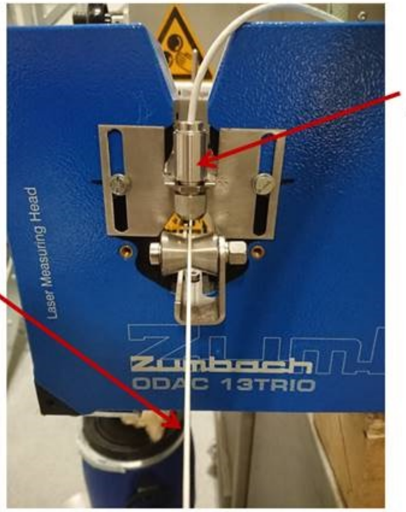
- Continuous manufacturing of tablets
- Combination of hot melt extrusion (HME) and direct compaction (DC) line
- Embedding of vitamin B1 as model API in Eudragit E PO as polymer carrier
- Compaction of pellets and excipients in DC line

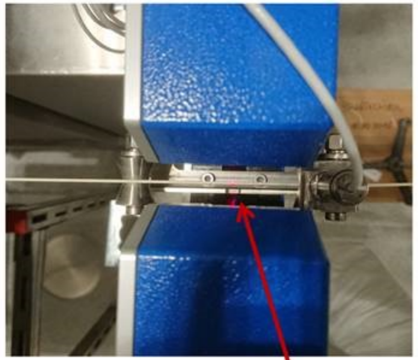
Continuous Tableting Process

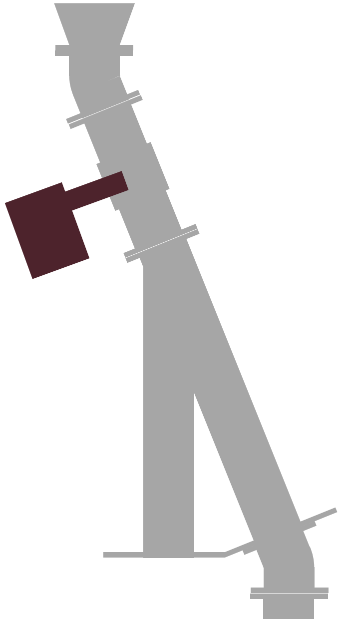


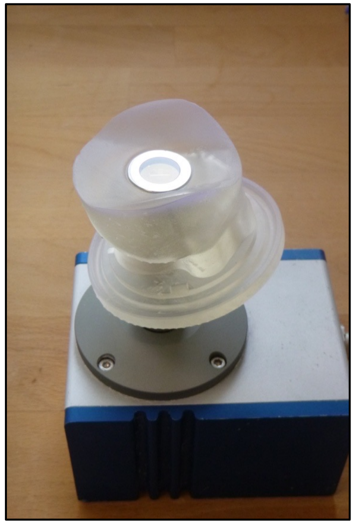
PAT Strategy and Tools

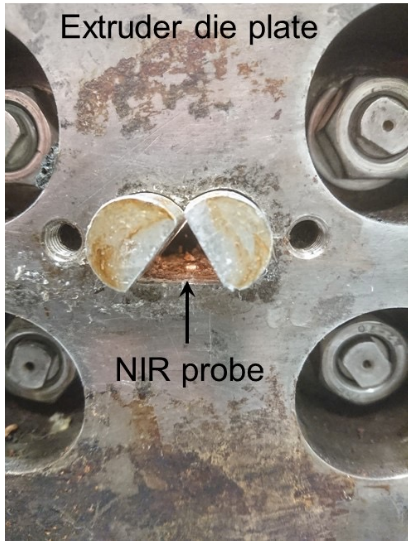
CQA	PAT method
Melt concentration	NIRS
Strand thickness	3-axis laser
Strand temperature	IR
Blend concentration	NIRS
Hopper level	Ultrasound



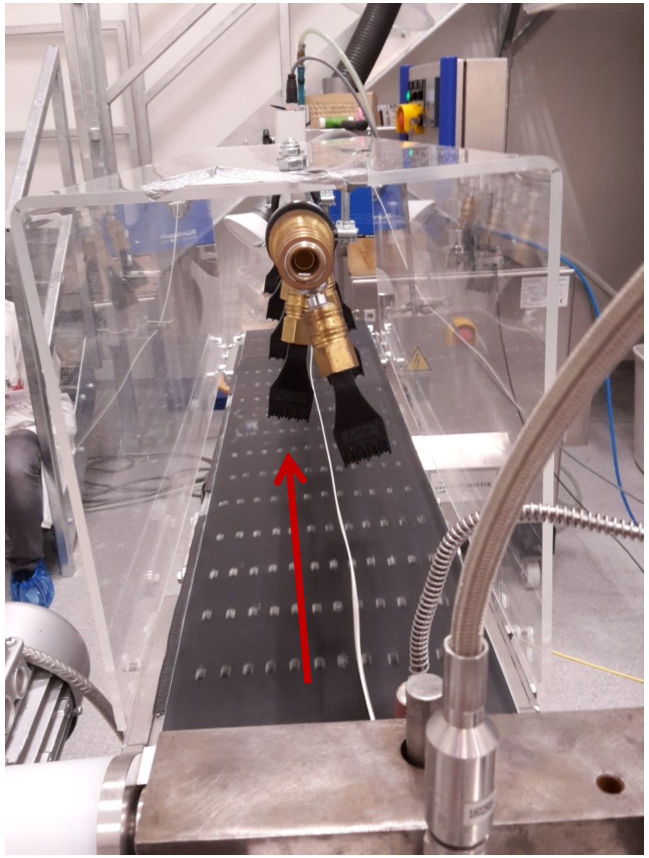


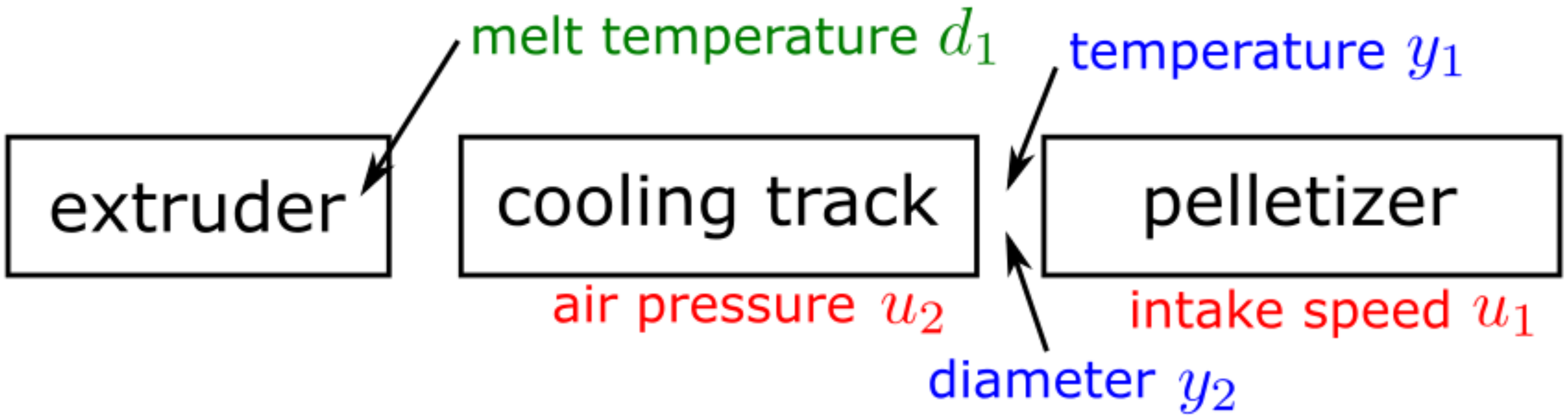




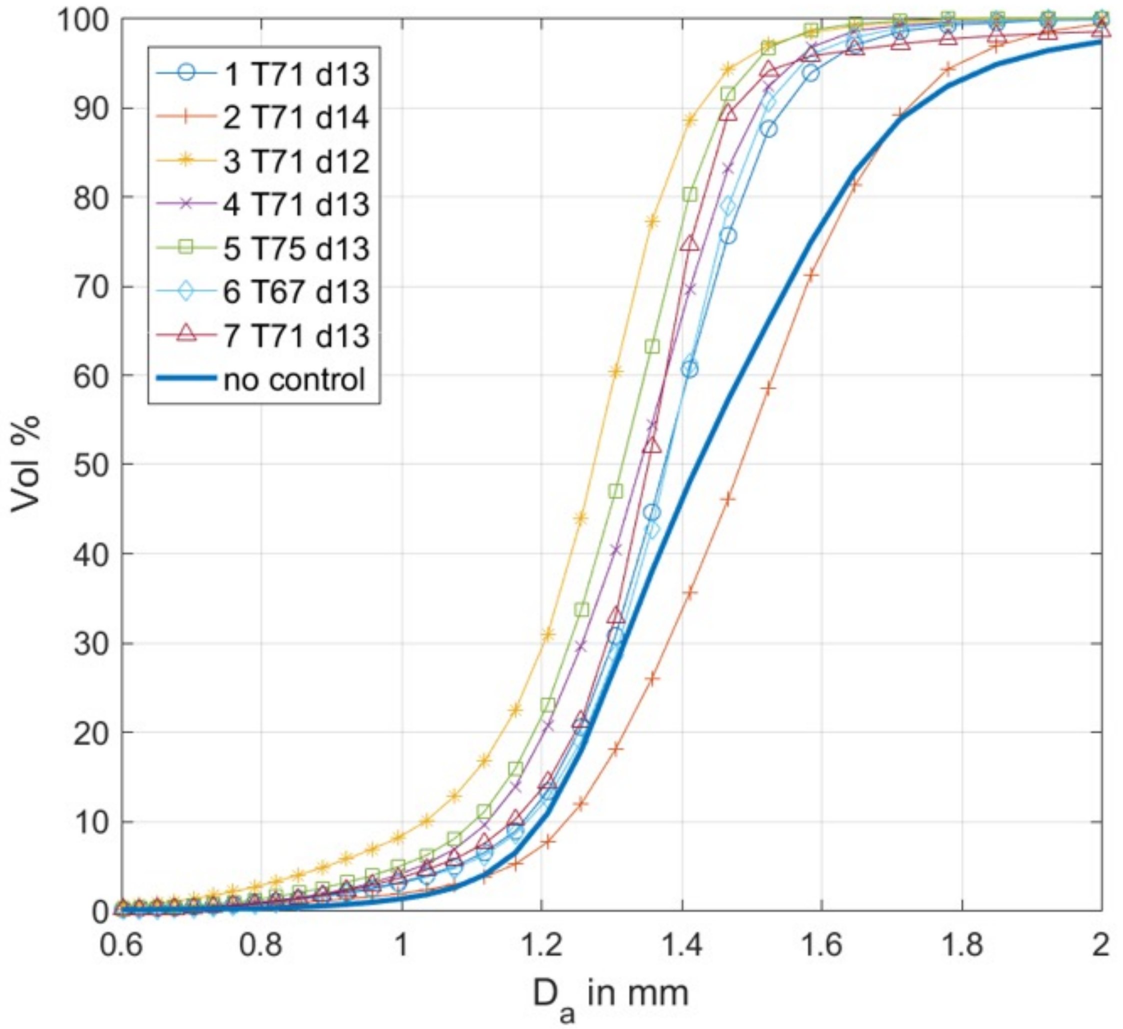


Model-predictive Control of Pelletization



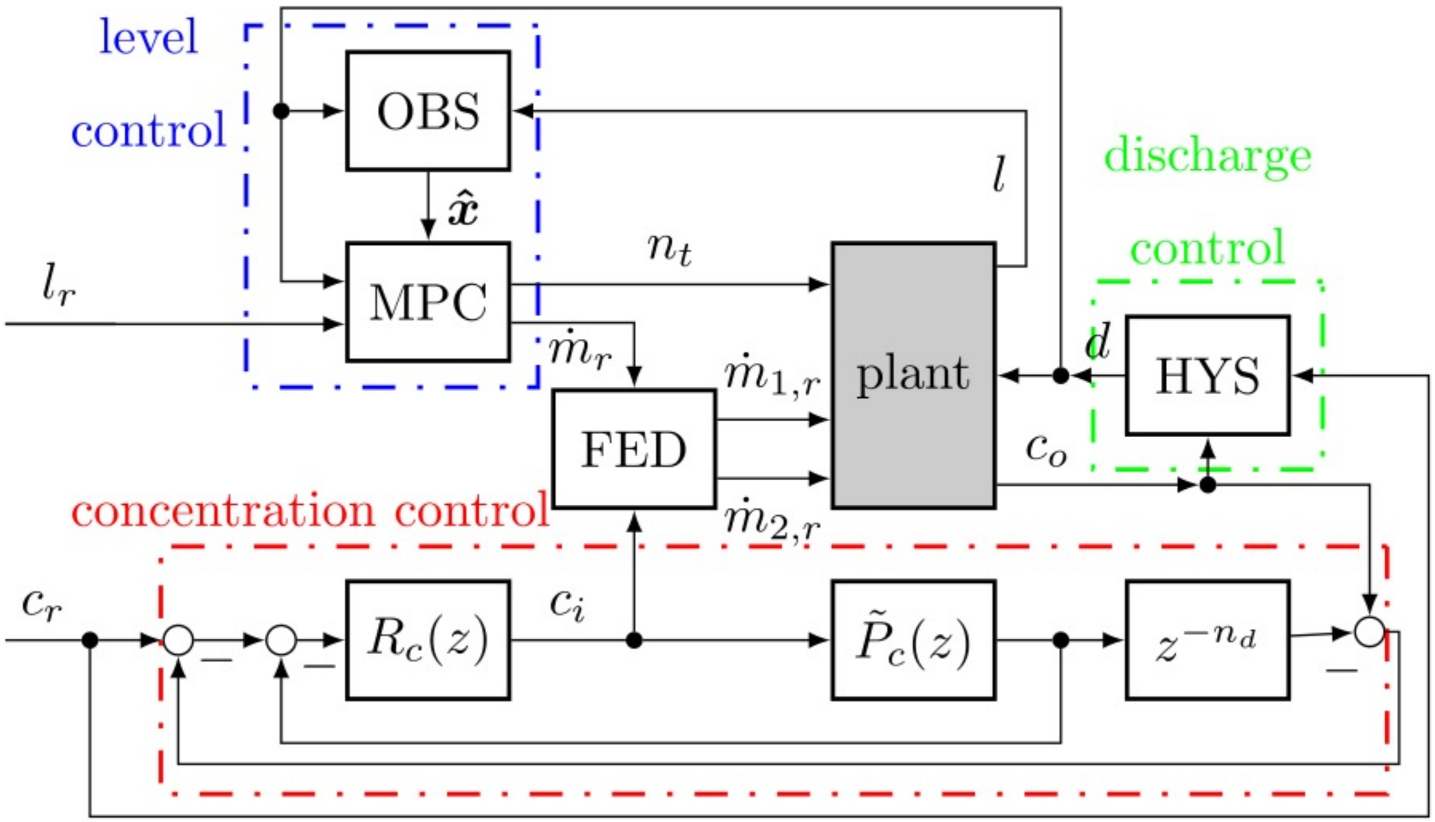


Model-predictive Control of Pelletization



- Strand diameter and temperature are the controlled variables
- Pelletizer intake speed and cooling air pressure are the manipulated variables
- Objective is a narrow particle size distribution (PSD) of the pellets
- Pelletization parameters are adjusted via MPC
- Influence of control is visible
- Obtained particle size distribution is narrower compared to process with no control

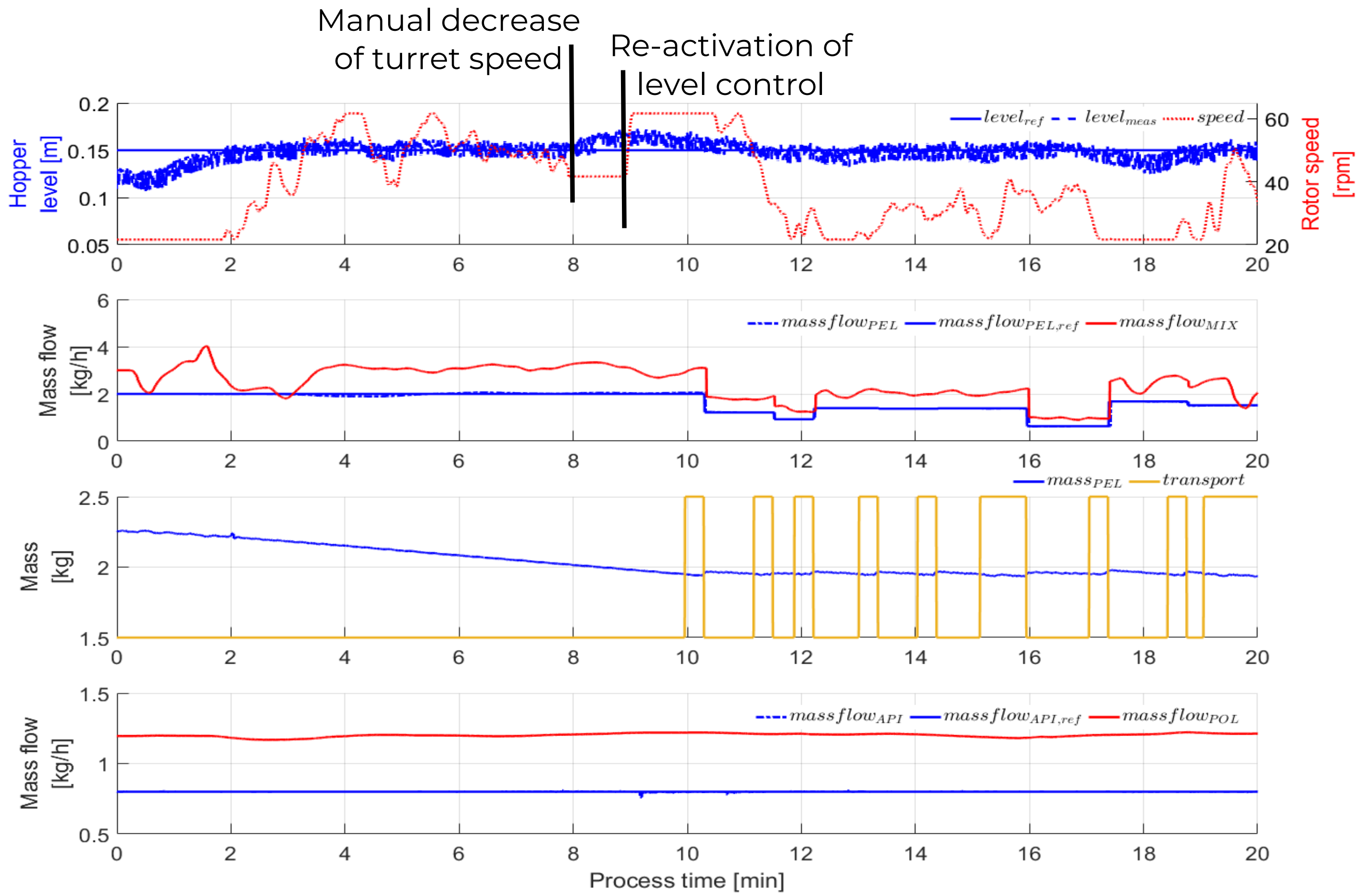
Model-predictive Control of Tableting Line



M. Kirchengast et. al. 2019, Ensuring tablet quality via model-based control of a continuous direct compaction process. Int. J. Pharm. 567, 118457. doi.org/10.1016/j.ijpharm.2019.118457

- Control concept for DC line
- Model-based control of
  - concentration (Smith predictor concept + PID controller R_c to adjust the ratio of the two solid feed rates)
  - OOS discharge (NIR measurement + threshold with hysteresis to trigger discharge)
  - tablet press hopper fill level (MPC to adjust total solid flow rate and turret speed of the tablet press)

Model-predictive Control of Tableting Line



Sacher et. al, 2019. Towards a Novel Continuous HME-Tableting Line: Process Development and Control Concept. Eur. J. Pharm. Sci 142, 105097. doi: 10.1016/j.ejps.2019.105097

- Rates of API and polymer feeders are kept at nominal values
- Mass hold-up in pellet feeder is started at higher level to test vacuum transport
- Rotor speed is adjusted manually after 8 min to increase hopper level
- Hopper fill level control is re-activated after 1 min and brings level back to nominal level of 150 mm

Conclusion & Next Steps

- A PAT strategy for an entire manufacturing line is essential to
  - monitor quality in-line and support RTRT
  - detect deviations from set-points and initiate control actions
  - support real-time process control
- Advanced real-time data based control concepts allow
  - a robust process even in the case of exceptional events, varying conditions and for start-up
  - consideration of different control objectives and specific constraints, e.g. maximize throughput or optimize equipment efficiency
  - automated operation and fault detection, highest level of control
- Running project "PharmComplete"
  - Combination of the complete manufacturing line (API synthesis, API processing and tablet manufacturing) at one single site
  - Development and implementation of full automation concept

Acknowledgements

The Research Center Pharmaceutical Engineering (RCPE) is funded within the framework of COMET - Competence Centers for Excellent Technologies by BMK, BMDW, Land Steiermark and SFG. The COMET program is managed by the FFG.

This work was funded by Austrian Research Promotion Agency FFG, within the program “Produktion der Zukunft”, project numbers 858704, 871458 and 891257.

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

Federal Ministry
Republic of Austria
Digital and Economic Affairs

FFG Promoting Innovation.

Das Land Steiermark

SFG NEUES DENKEN. NEUES FÖRDERN.

Let‘s continue the conversation.

stephan.sacher@rcpe.at
+43 316 873 30959