

Validation report on NMR

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DOCUMENT DETAILS

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Abstract: The departure from the current automation landscape to next generation automation concepts for the process industry has already begun. Smart functions of sensors simplify their use and enable plug-and-play integration, even though they may appear to be more complex at first sight. Smart sensors enable concepts like self-diagnostics, self-calibration, and self-configuration/ parameterization whenever our current automation landscape allows it.

Here we summarize the currently discussed general requirements for process sensors 4.0 and introduce a smart online NMR sensor module as example, which was developed for an intensified industrial process funded by the EU's Horizon 2020 research and innovation programme (www.consens-spire.eu).

Keywords: Online NMR sensor; Nuclear Magnetic Resonance Spectroscopy; Process Analytical Technology; Smart Sensor; Industry 4.0; Industrial Internet of Things; Process Industry; Process Control

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3	20.12.2017	Revision 02	BAM
4	21.12.2017	Final version	BAM
5	24.01.2018	Final version – Literature updates with URNs	BAM

ACRONYMS AND DEFINITIONS

ACRONYMS	DEFINED AS
NMR	Nuclear Magnetic Resonance (Spectroscopy)
IHM	Indirect Hard Modeling
PLS-R	Partial Least Squares Regression

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1 Description of Deliverable D1.9

1.1 Validation Report on NMR

Deliverable D1.9 is described in Annex 1, 1.3.3 WT3 under WP1 as follows:

“Validation report on NMR [33] – The results of experiments using the NMR sensor for case 1 (INVITE) and subtask 1.2.3 (BASF) are summarised to a final validation report.”

1.2 Reports on Subtasks for the NMR Sensor Development

In the same chapter, Task 1.2 “NMR sensor development” is described as follows:

“>>> Task 1.2 NMR sensor development <<<

(BAM, TNO, INV, BASF, ARK); this task aims at the development of an On-line measurement technique to measure the chemical composition of the products of case 1 and case 2. The work is divided in 2 subtasks:

- Subtask 1.2.1 Hardware development including control (BAM); this subtask consists of the development of a field instrument having a flow through cell with ATEX compatibility working as automated online instrument with a sample bypass which can be used in field in direct vicinity of the sample source. The field instrument is controlled by a PLC and includes communication to a process operating.

- Subtask 1.2.2 Development automated data preparation and analysis (BAM, TNO); this subtask consists of the development of automated data preparation and analysis. Spectral raw data will be Fourier transformed and prepared in order to provide a reproducible and proper baseline correction, phasing, line shape, and normalization. Transformed spectra will be analysed automatically with chemometric models

Subtask 1.2.3 Experimental verification of concept for polymers (case 2); In order to investigate suitability of NMR for measurements on the high viscous polymers, BASF laboratories will be used to perform verification trials (Task 1.5).”

2 Concept and Validation of the NMR Sensor at BAM

2.1 Concept for a Smart NMR Sensor

2.1.1 Introduction

The future competitiveness of the process industry and their providers depends on its ability to deliver high quality and high value products at competitive prices in a sustainable fashion, and to adapt quickly to changing customer needs. Competitiveness therefore means safeguarding of the required product quality with an optimum use of equipment, raw materials, and energy.

Process analytical techniques are extremely useful tools for chemical production and manufacture particularly for the pharmaceutical, food, and (petro-) chemical industries. It can be easily transferred to manufacturing for

process control and for quality assurance of final products to meet required product specifications, since it provides dynamic information about product properties, material stream characteristics, and process conditions. [1, 5]

2.1.2 Process Control Based on Intelligent Field Devices

Intelligent field devices, digital field networks, Internet Protocol (IP)-enabled connectivity and web services, historians, and advanced data analysis software are providing the basis for the future project “Industrie 4.0” and Industrial Internet of Things (IIoT). This is a prerequisite for the realization of Cyber-Physical Systems (CPS) within these future automation concepts for the process industry. “Cyber-Physical Systems are integrations of computation with physical processes. Embedded computers and networks monitor and control the physical processes, usually with feedback loops where physical processes affect computations and vice versa”. [2, 5]

2.1.2.1 Integrated Process Design and Intensified Processes – Need for Smart Field Devices

Novel discoveries, developments, and concepts in the field of process engineering and in particular process intensification are currently promoted for analysis and design of innovative equipment and processing methods. This leads to substantially improved sustainability, efficiency, and environmental performance, alternative energy conversion, alternative transport mechanisms, intensified hydrodynamics, structured environments, multi functionality, and intensified plant operation.

Intensified continuous processes are in focus of current research. Compared to traditional batch processes, intensified continuous production gives admittance to new and difficult to produce compounds (see Section 3. as an example), leads to better product uniformity, and drastically reduces the consumption of raw materials and energy. Flexible (modular) chemical plants can produce various products using the same equipment with short down-times between campaigns, and quick introduction of new products to the market. Typically, such plants have smaller scale than plants for basic chemicals in batch production but still are capable to produce kilograms to tons of specialty products each day.

Consequently, full automation is a prerequisite to realize such benefits of intensified continuous plants. In continuous flow processes, continuous, automated measurements and tight closed-loop control of the product quality are mandatory. If these are not available, there is a huge risk of producing large amounts of out-of-spec (OOS) products.

In pharmaceutical production, the common future vision is “continuous manufacturing” (CM), based on “Real Time Release” (RTR), i.e., a risk based and integrated quality control in each process unit. This will allow for flexible hook-up of smaller production facilities, production transfer towards fully automated facilities, less operator intervention, less down time, and end to end process understanding over product lifecycle, future knowledge, and faster product to market. It is also assumed to significantly reduce the quality control costs within a CM concept at the same time.

2.1.2.2 Lack of Contemporary Process Control Concepts in Our Current Automation Landscapes

Current focuses of research are closed-loop adaptive control concepts for plant-wide process control, which make use of specific or non-specific sensors along with conventional plant instruments. Such advanced control solutions could give more information than only control information, such as sensor failure detection, control performance monitoring, and improve simulation-based engineering as one of the concepts in Industry 4.0 or IIoT.

With the introduction of advanced process analytical technology, the closeness of key process variables to their limits can be directly monitored and controlled and the processes can automatically be driven much closer to the optimal operating limit. Classical, non-model-based solutions reach their limits when sensor information from several sources must be merged. In addition, their adaptation causes a high effort during the life cycle of the process. This highlights the need for adaptive control strategies, which are based on dynamic process models

as mentioned above. Model-based control concepts have also the potential to automatically cope with silent changes of the raw-materials as well as process conditions.

Chemical process control technology has advanced significantly during the last decades. For world-scale high-throughput continuous processing units such as crackers and separation trains, in most cases classically engineered control solutions have been replaced by model-based techniques, most prominently model-predictive control (MPC) based on linear plant models. However, the engineering and implementation costs of such advanced controllers are still high. For smaller, flexible processes in which varying products or intermediates are manufactured, it is not economic to re-engineer the control concept or to re-model the process for all intended processes – especially for a modular approach.

Chemometric techniques for the derivation of empirical models (e.g., PLS (Partial Least Squares), PCA (Principal Component Analysis)) are available but currently mostly used for off-line data analysis to detect the causes of variations in the product quality. An automated application along the life cycle is still very limited. Up to now the development of such models requires significant experimental work. The use of first principles methods (e.g., spectroscopic models, cf. Section 2.3.4) along with reduction of the effort needed for these experiments is focus of ongoing research. When such stationary models are available and are combined with dynamic models that describe the times needed for the transition from one steady state to the other, feedback control and iterative optimization schemes can be built. Making use of novel sensors, like online NMR, tremendously promote the use of novel process control concepts.

2.1.2.3 Current and Future Requirements to Process Sensors and Actuators

Sensors are the sense organs of process automation. At present, there are serious changes in the areas of information and communication technology, which offer a great opportunity for optimized process control and value added production with dedicated network communicating sensors. These kinds of “smart” sensors provide services within a network and use information from it. Consequently, smart process sensors enable new business models for users, device manufacturers, and service providers.

Recently the technology roadmap “Process Sensors 4.0” was published [3], which identifies the necessary requirements as well as the communication abilities of such process sensors – from a simple temperature sensor up to current technologies, which are in development. Important smart features are depicted in Fig. 1.

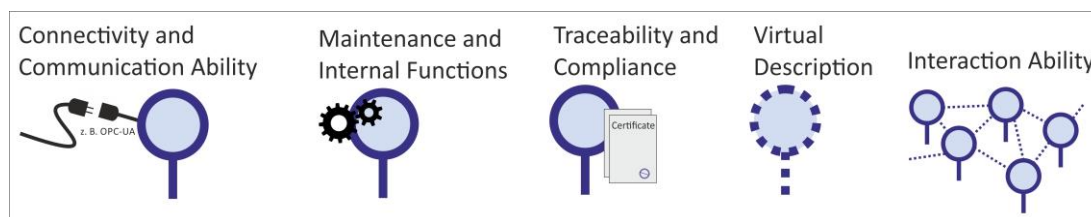


Figure 1. Most important features of a smart sensor or actuator [3]

The cost of connectivity is dropping dramatically, providing powerful potential to connect people, assets, and information across the industrial enterprise. While only providing add-on information, the first cloud services may not require a high disposability or real-time capabilities. But are these given in future, even process control tasks were possible using cloud services, e.g., when complex computing algorithms are needed, which require computing power.

2.1.3 “Chemistry for Chemistry” – Smart Compact NMR Spectroscopy in Process Control

Monitoring specific information (i.e., “chemical” such as physico-chemical properties, chemical reactions, etc.) is the key to “chemical” process control. As an example, a given pharmaceutical aromatic coupling reaction step

(lithiation reaction) was investigated. [4, 5] The challenge within the project was to integrate a commercially available low-field NMR spectrometer [11] from a laboratory application to the full requirements of an automated chemical production environment including robust evaluation of sensor data.

Today, mainly optical online methods are applied. Quantitative online nuclear magnetic resonance (NMR) spectroscopy has a high potential for direct loop process control of fluid process streams [1, 3, 5] since it provides rapid and non-invasive information when applied in a flow through mode. One of the most attractive features of quantitative NMR spectroscopy is that NMR peak areas can be directly used for concentration quantification without further calibration – if complete spin magnetisation is achieved. A major advantage of NMR spectroscopy is that the method features a high linearity between absolute signal area and sample concentration, which makes it an absolute analytical comparison method which is independent of the matrix. This is an important prerequisite for robust data evaluation strategies within a control concept and reduces the need for extensive maintenance of the evaluation model over the time of operation.

2.2 Hardware Development including Control

The work described here is according to the abovementioned subtask 1.2.1: Hardware development including control (BAM); this subtask consists of the development of a field instrument having a flow through cell with ATEX compatibility working as automated online instrument with a sample bypass which can be used in field in direct vicinity of the sample source. The field instrument is controlled by a PLC and includes communication to a process operating.

2.2.1 Concept for the Field Integration of a Benchtop NMR Spectrometer with ATEX Certification

The developed smart NMR sensor had to be provided in an explosion proof housing, which involves a compact 43.5 MHz NMR spectrometer [11] from Magritek, Aachen, together with an acquisition unit and a programmable logic controller for fully automated data preparation (phasing, baseline correction) and quantitative evaluation. The requirements were collected prior to this task in deliverable D1.10 “Procedure for PAT sensor requirements specification”, which is publicly available [6].

In order to integrate the non-explosion proof benchtop NMR spectrometers into the real process environment special attention had to be paid on explosion protection guidelines and automation of signal processing (data pre-treatment, evaluation and communication to the process control system). The transfer of firmware data from the instrument had to be realized directly via an embedded PC for DIN rail systems or via an interface to external computing facilities, such as virtualized environments.

The requirements for electrical equipment for areas subject to explosion are described amongst others by ATEX (European guideline) or by IECEx (international commission). Depending on the type of materials that arise in the process, the frequency and duration of the occurrence of these materials, different protective requirements for the resources arise. Therefore, areas subject to explosion are divided into 6 different danger zones, according to CENELEC and IEC. According to the zone allocation, using the device category it can be derived which resources may be used in a zone. In order to specify for which zone a resource may be used, the device group and device category are relevant. Using the temperature classes, device and explosion groups a suitable protection principle, e.g., pressure encapsulation, can be set up. However, at the same time it had to be kept in mind to remove the heat accumulated in the explosion proof housing, to keep the magnet at constant temperature. Otherwise temperature fluctuations in the permanent magnet will cause the B_0 field to vary and hence cause a shift in the resonance frequency of the nuclei.

Luckily BAM had a strong partner for all ATEX discussions in its sister institute Physikalisch-Technische Bundesanstalt (PTB), Braunschweig and Berlin [7] according to the norms EN 60079-0:2012, EN 60079-2:2015, leading to the concept, which is depicted in Figures 2 and 3.

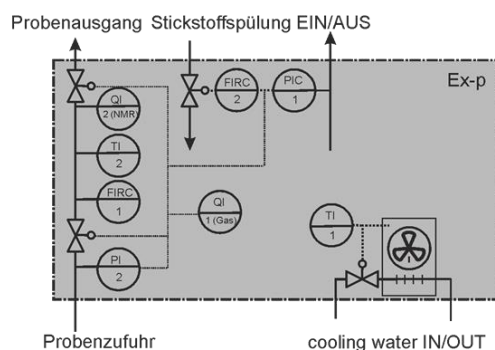


Figure 2. Final concept of the sample bypass (Probenzufuhr = sample inlet, Probenausgang = sample outlet), nitrogen purge (Stickstoffspülung), and cooling system for the online NMR analyzer module. The sample bypass had to be equipped with two (normally closed) shut off valves, which are only activated within the correct temperature and pressure regions and are closed automatically on leakage detection.

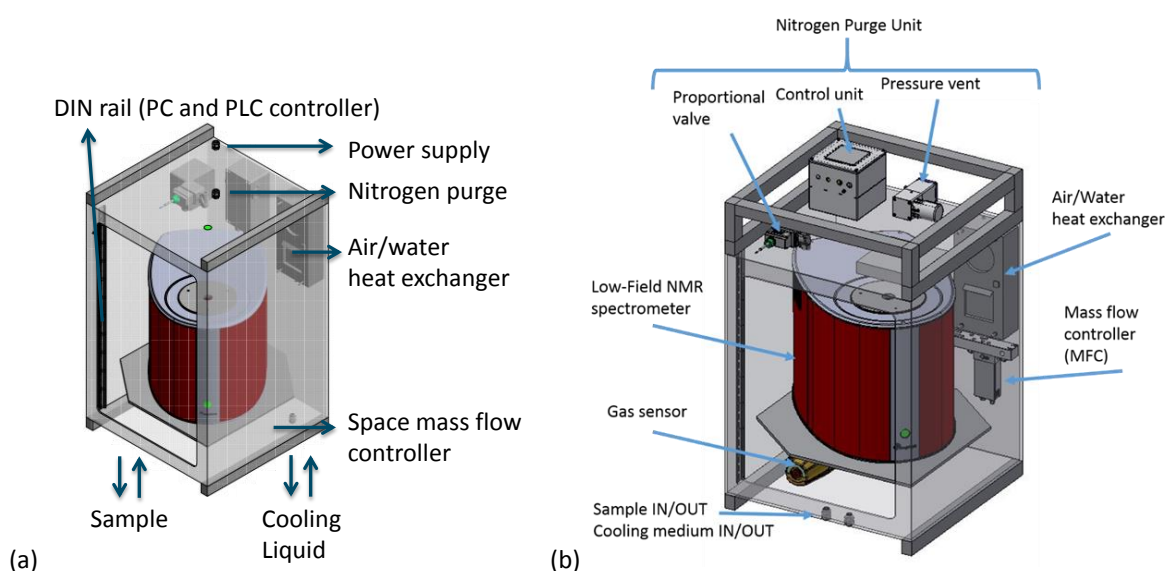


Figure 3. First (a) and final (b) concept of the ATEX box for the online NMR analyzer module [11] with an outer module size of $57 \times 57 \times 85$ cm. The analyzer contains an optical gas sensor for leakage control of the solvent used, a mass flow controller to provide the optimal quantitative flow velocity for NMR experiments, and an Air/Water heat exchanger to provide a constant ambient temperature (Source: BAM)

Upon this concept, BAM had received an offer from AGT-PSG GmbH & Co.KG in Steinbach, Germany [8] for the construction and provision of the pressurized enclosure and mounting of corresponding equipment according to the ATEX discussions with PTB. The manufacturing part of that manufacturer took about 10 weeks (see Fig. 4).

The construction and provision of the pressurized enclosure included EC Declaration of Conformity as well as an EC Low voltage Directive certificate (see Fig. 5a). This was the basis for an operator manual, issued by BAM (see Fig. 5b), which contained detailed instructions upon general use, installation, requirements and basic as well as maintenance operation of the NMR analyzer module. Finally, an ATEX certificate was issued based on the abovementioned documents (see Fig. 5c).

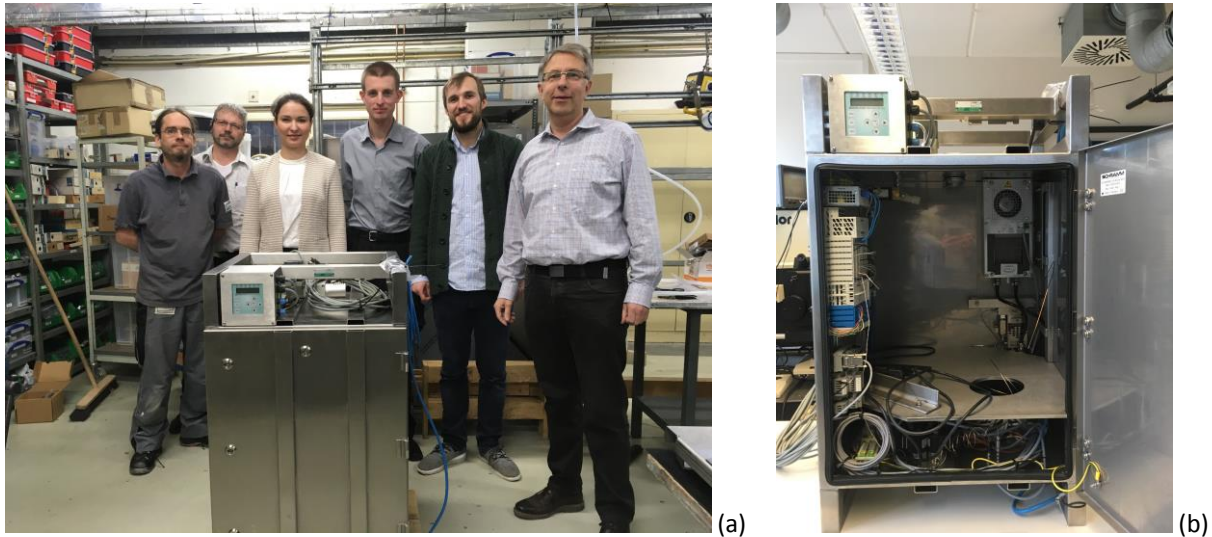


Figure 4. (a) Pick up of the pressurized enclosure according to the ATEX requirements (EX II 2G Ex pxb db ib IIB T3 Gb) from AGT-PSG GmbH & Co.KG in Steinbach on 26.01.2017 (Source: AGT-PSG GmbH & Co.KG); (b) Detail of opened enclosure for the NMR sensor of 57 × 57 × 85 cm module size (Source: BAM).

2.2.1.1 Explosion Protection Classification

- Zone classification: Zone 1
- Explosion group: IIB (THF: maximum experimental safe gap = 0,87 mm, ignition temperature = 230 °C)
- Temperature class: T3
- Vapor pressure: 173 hPa (20 °C)
- Lower Explosion limit: 1,5 Vol.-%, 46 g/m³
- Upper Explosion limit: 12,4 Vol.-%, 370 g/m³

Finally the certificate of conformity was issued from Physikalisch-Technische Bundesanstalt, Braunschweig und Berlin according to the norms EN 60079-0:2012, EN 60079-2:2015 (see Fig. 5c).

The achieved conformity is: II 2 G Ex pxb db ib IIB T3 Gb



Figure 5. Overview on documentation: (a) EC Declaration of Conformity as well as an EC Low voltage Directive certificate (left); (b) operator manual, issued by BAM (middle); (c) PTB ATEX certificate (right)

2.2.2 Concept for the Field Communication of the Online NMR Analyzer Module

As mentioned above, the online NMR analyzer module should serve a conventional process control system, which is currently mainly based on 4–20 mA connections as well as a future process control environment, which is believed to communicate bidirectionally to a process control system. This is depicted in Fig. 5.

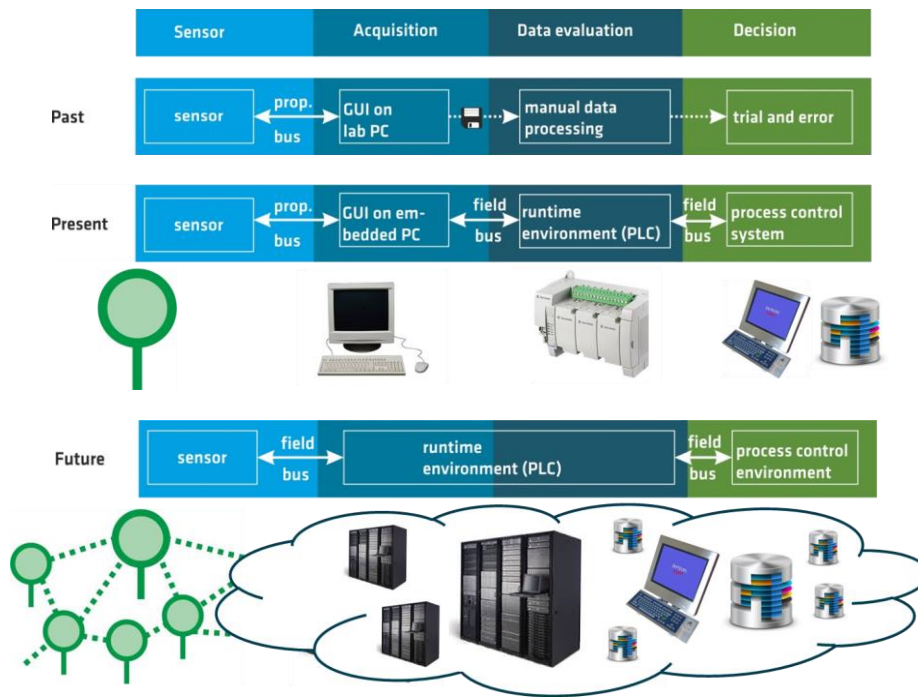


Figure 5. Data flow chart for reaction monitoring in past and recent laboratory applications (top) will have to be changed for process control (middle and bottom) according to [1].

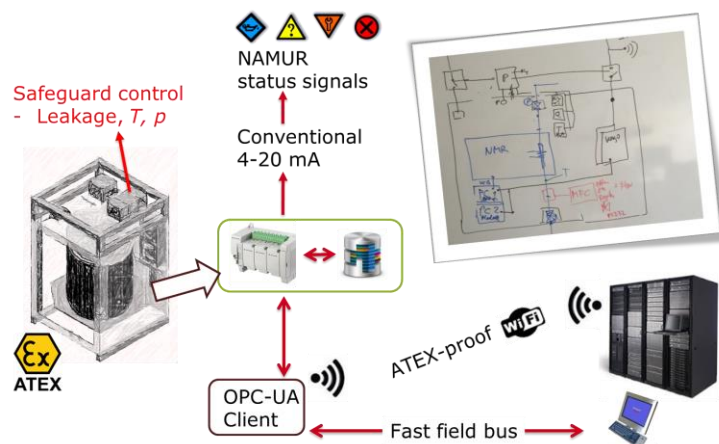


Figure 6. First communication concept of the online NMR analyzer serving conventional 4–20 mA connections as well as future automation concepts based on OPC-UA connections over intrinsically safe Ethernet cable or a Wi-Fi connection (according to Fig. 5).

It is proposed, that sensor data analysis will in future grow together with advanced control technology. In addition, these tasks will move from embedded PCs and programmable logic controllers towards (virtual) runtime environments and that process control systems will accordingly change to process control environments.

The first communication concept therefore integrated the conventional world as well as the Industry 4.0 world. In addition to the NMR information (see 2.3 for data acquisition, preparation, and analysis concepts) further controller data (e.g., temperature, pressure, flow rate, etc.), should be derived for monitoring, control, and maintenance tasks as well for fail-safe control. Results should be shared unidirectionally with process control systems via conventional 4–20 mA connections (for compatibility to current automation landscapes) as well as bidirectionally with an integrated OPC-UA server over intrinsically safe Ethernet cable or Wi-Fi connection.

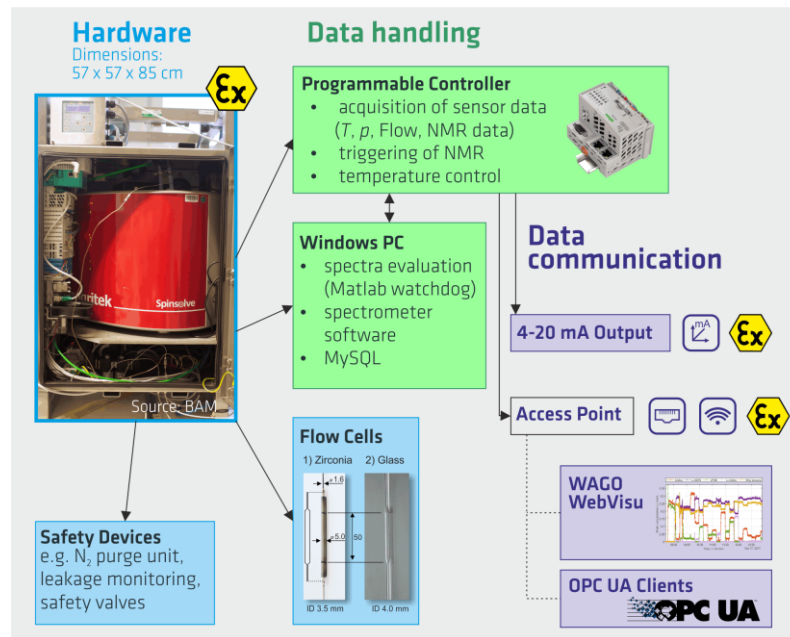


Figure 7. Final communication scheme of the online NMR analyzer.

The final communication scheme of the online NMR analyzer is depicted in Fig. 7. All data is exchanged to a MySQL database running on an onboard Windows PC. This PC also maintains the spectrometer software as well as an instance of spectral data preparation and analysis software, based on Matlab (see Chapter 2.3). The data is accessed by a programmable logic controller, which is used for the acquisition of addition sensor information such as, e.g., temperature, mass flow, or pressure, for triggering of the NMR spectrometer as well as for data communication via the abovementioned conventional 4–20 mA connections or OPC-UA based communication over intrinsically safe Ethernet cable or Wi-Fi connection (see Fig. 7).

Via the OPC-UA based communication over intrinsically safe Ethernet cable or Wi-Fi connection the sensor can be fully integrated into current data communication concepts. One way is the communication with the WAGO “WebVisu”, which is a graphical user interface according to Codesys 3.0 standards operation under HTML browsers. The graphical user interface supports a standard mode, where the setpoints and the mass flow data as well as temperature and pressure are depicted together with the computed NMR sensor information. In a maintenance mode with restricted access, the sensor owner can run maintenance tasks, such as shimming and set-up of the NMR instrument, changing set-points of the mass flow controllers and others. An example of the maintenance mode is depicted in Fig. 8. Another way is the communication via OPC-UA clients, which was used within the validation test runs of the sensor (see below). Within the project, OPC-UA clients such as LabView, Matlab and others were successfully used. For instance, OPC-UA information was shared with the advanced process control systems of our partners from TU Dortmund to compute optimal set-points of the mass flow controllers

within the plant. More detailed descriptions of these results are currently in preparation and will be published in near future on the project website (www.spire-consens.eu).

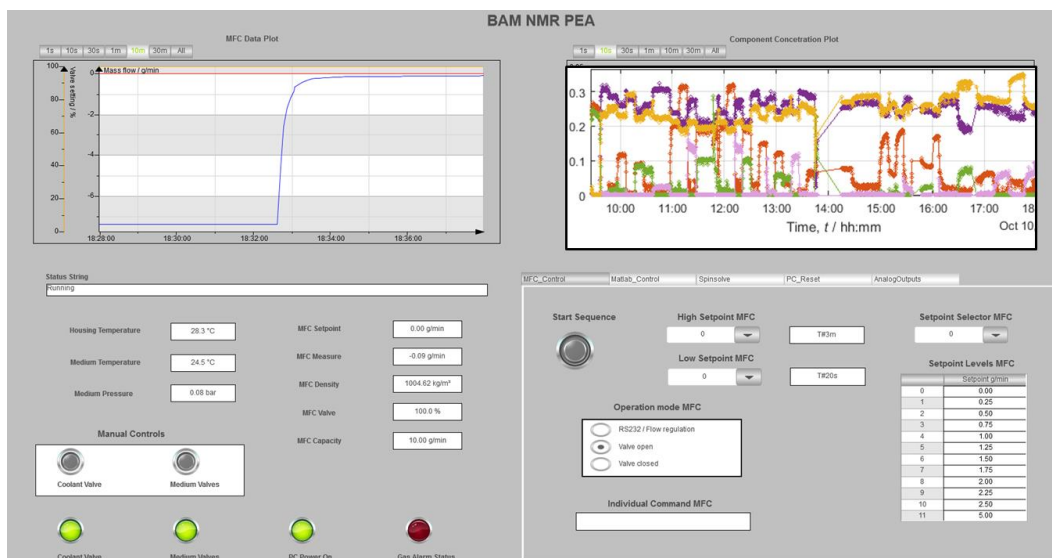


Figure 8. Example for the WAGO “WebVisu” graphical user interface in the maintenance mode. Important sensor information such as, e.g., temperature, mass flow, status information on the NMR spectrometer, or pressure are given in the bottom left section. The upper left diagram displays mass flow set-points and current mass flow, the upper right section displays five individual analyte concentrations, measured by NMR and the bottom right section allows for maintenance tasks, such as shimming of the NMR instrument or changing NMR spectrometer analysis methods.

2.3 Development Automated Data Preparation and Analysis

The work described here is according to subtask 1.2.2: Development automated data preparation and analysis (BAM, TNO); this subtask consists of the development of automated data preparation and analysis. Spectral raw data will be Fourier transformed and prepared to provide a reproducible and proper baseline correction, phasing, line shape, and normalization. Transformed spectra will be analysed automatically with chemometric models

2.3.1 Continuous Pharmaceutical Reaction Step in a Modular Plant as Case Study for Fully Automated NMR Data Analysis

Compared to traditional batch processes, intensified continuous production gives admittance to new and difficult to produce compounds (see reaction Fig. 9 as an example), leads to better product uniformity, and drastically reduces the consumption of raw materials and energy. Flexible (modular) chemical plants can produce various products using the same equipment with short down-times between campaigns, and quick introduction of new products to the market. Typically, such plants have smaller scale than plants for basic chemicals in batch production but still are capable to produce kilograms to tons of specialty products each day.

Consequently, full automation is a prerequisite to realize such benefits of intensified continuous plants. In continuous flow processes, continuous, auto-mated measurements and tight closed-loop control of the product quality are mandatory. If these are not available, there is a huge risk of producing large amounts of Out-of-Spec (OOS) products.

In pharmaceutical production, the common future vision is Continuous Manufacturing (CM), based on Real Time Release (RTR), i.e., a risk-based and integrated quality control in each process unit. This will allow for flexible

hook-up of smaller production facilities, production transfer towards fully automated facilities, less operator intervention, less down time, and end to end process understanding over product lifecycle, future knowledge, and faster product to market. It is also assumed to significantly reduce the quality control costs within a CM concept at the same time.

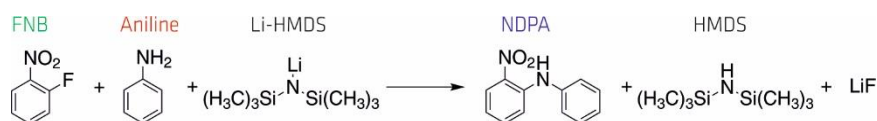


Figure 9. Reaction scheme: FNB: 1- fluoro-2-nitrobenzene, Li-HMDS: Lithiumbis(trimethylsilyl) amide, NDPA: 2-nitrodiphenylamine. Aniline was also replaced by *p*-toluidine and *p*-fluoroaniline.

Fig. 9 represents a given example of a pharmaceutical reaction step, within two aromats are coupled using the lithium base Li-HMDS. The reaction takes place in a 5 wt-% solution in tetrahydrofuran. Deviations from unknown starting material and reactant concentrations together with the precipitation of LiF will lead to severe fouling and blocking of the modules. Typically, metal organic reactants are difficult to analyze due to the sensitivity to air and moisture. Thus, this example reaction was chosen in CONSENS to develop and validate a compact NMR sensor to maintain an optimal stoichiometry during the full course of the continuous production.

2.3.2 Smart Compact NMR Spectroscopy in Process Control

Monitoring specific information (such as physico-chemical properties, chemical reactions, etc.) is the key to chemical process control. The challenge within the project and its given lithiation reaction was to integrate a commercially available low-field NMR spectrometer [1] from a laboratory application to the full requirements of an automated chemical production environment including robust evaluation of NMR spectral data.

The NMR analyzer involves a compact 43.5 MHz NMR spectrometer together with an acquisition unit and a programmable logic controller for automated data preparation (phasing, baseline correction) as well as data evaluation. Therefore, the aromatic region of the NMR spectra in Fig. 10 had to be chosen; representing higher order NMR spectra.

In a first approach, a couple of semi batch reactions were performed for development of Partial Least Squares Regression (PLS-R) as well as Indirect Hard Modeling (IHM) models [10]. Within these studies Li-HMDS was dosed stepwise to the reactants aniline and FNB in a batch reactor to produce spectral data material along the reaction coordinate. The reaction was in parallel observed using 500 MHz high-field NMR spectroscopy as reference method.

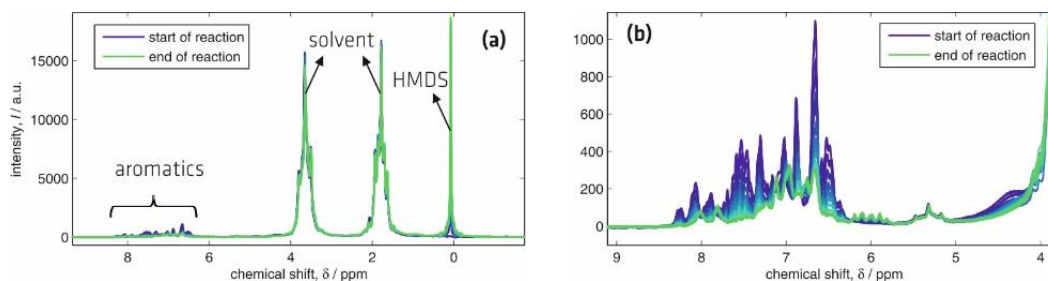


Figure 10. (a) Complete low-field NMR spectrum (43.5 MHz, single scan) and (b) aromatic region of automatically phased, baseline corrected, and shift corrected proton spectra for the lithiation reaction.

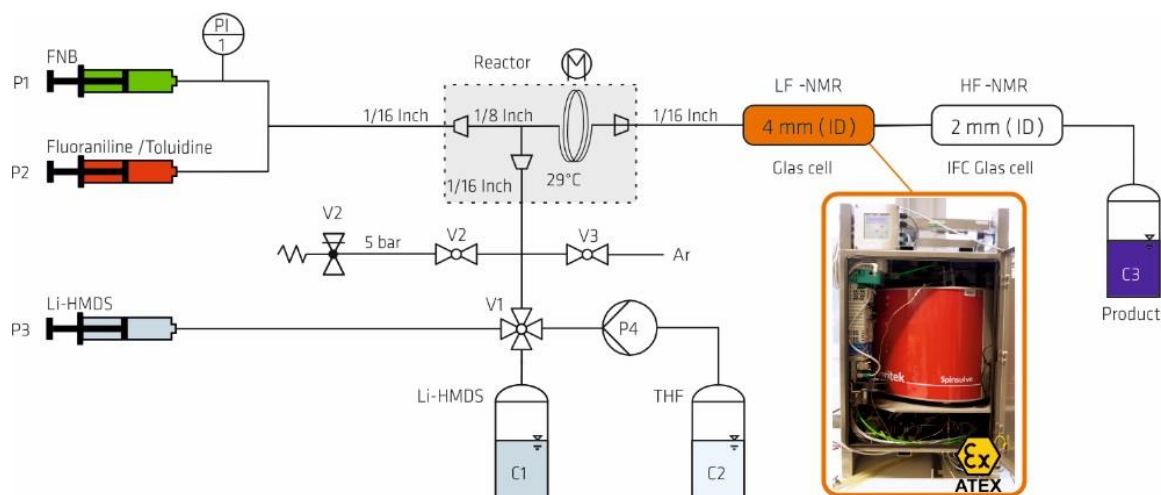


Figure 11. Scheme of the validation set-up for monitoring of the continuous reaction unit with the compact NMR sensor (orange box). The lithiation reaction (Fig. 9) is continuously carried out in a thermostated 1/8" tubular reactor using syringe pumps. HF NMR spectroscopy (upper right) served as reference

For validation purposes, the set-up depicted in Fig. 11 was used for monitoring of the continuous lithiation reaction in a thermostated 1/8" tubular reactor using syringe pumps. The set-up was matched to the reaction conditions of the actual plant. It was used to validate the PLS-R and IHM models as described below – again using high-field NMR spectroscopy as reference method. A considerable number of continuous experiments were performed for validation taking account for various reaction conditions by individually adjusting the flow rates of the reagents aniline, FNB, and Li-HMDS [10].

2.3.3 Data Analysis Methods

Chemometrics for the derivation of empirical models, e.g., PLS-R or PCA (Principal Component Analysis) is available and state of the art in reaction and process monitoring. Automated applications along the life cycle are still very limited. Up to now the development of such models requires significant experimental work, i.e., producing data from several time-consuming calibration runs, ideally via experimental plans (DoE) [10].

2.3.4 Physically Motivated Spectral Models

The use of so-called First Principles methods along with reduction of the effort needed for these experiments is focus of ongoing research. Making use of novel sensors, like online NMR, in combination with flexible data analysis methods like IHM tremendously promote the use of novel process control concepts [1, 5, 9, 10].

IHM model development consists of three steps: Firstly, pure component models are built upon NMR spectra of the reactants and products (Fig. 12a). Each pure component model (Hard Model) consists of a number of Lorentzian-Gaussian functions, representing the spectral peaks [9, 10].

Within that Hard Model, the ratio of peak areas are fixed against each other. Secondly, an experimental NMR spectrum is acquired and prepared by phasing and baseline correction (Fig. 12b). Finally, this experimental spectrum is represented by the given pure component models (Component Fitting) from the beginning step by iterative fit routines aiming at minimized residues (Fig. 12c). Within this step, selected parameters of Lorentzian-Gaussian functions such as position, height, or width can be optimized. This allows for slight line shifts or other non-linear effects along the course of the reaction, which likely occur in NMR spectra of technical mixtures and make IHM the method of choice.

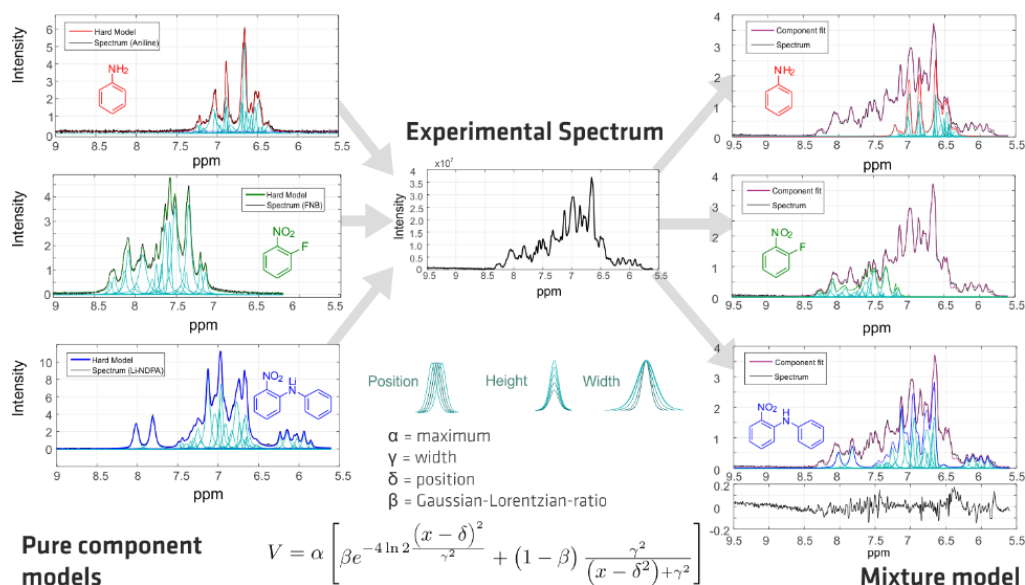


Figure 12. Data analysis scheme for Indirect Hard Modeling (IHM) of the aromatic region (see Fig. 10) of the NMR spectrum. (a) Pure Component Models (left); (b) Experimental Spectrum (middle); (c) Mixture Models (right).

Fig. 13 depicts how physically motivated spectral models based on quantum mechanical calculations can be used to derive the pure component models, shown for aniline. Therefore, line spectra from spin calculations were adopted by empirically fitting their line shape to the real pure component spectrum.

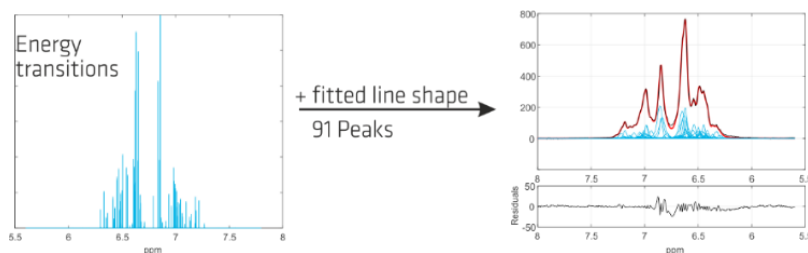


Figure 13. Calculation of pure component model based on spin calculations (NMR Solutions, Kuopio).

2.4 Experimental Verification of Concept

The work done is according to subtask 1.2.3: Experimental verification of concept for polymers (case 2); In order to investigate suitability of NMR for measurements on the high viscous polymers, BASF laboratories will be used to perform verification trials (Task 1.5) as well as tasks in WP 4 (which are internally described in detail in D4.4: Final report describing the results from the validation)

2.4.1 Laboratory Validation of the Data Preparation and Analysis Concept at BAM

Figure 14 shows the amount of substance fractions observed with the LF NMR sensor and the IHM methods according to a Design of Experiments (DoE) over an observation period of 6.5 hours in comparison with HF NMR data. In some runs aniline was replaced by *p*-toluidine or *p*-fluoroaniline (Figures 9 and 11) in order to test the modular IHM approach. In all cases, the pure component models were exchangeable and worked together with

the remaining models for FNB. In general, all results found by IHM are in good agreement with results from the PLS-R model as well as the HF NMR reference data.

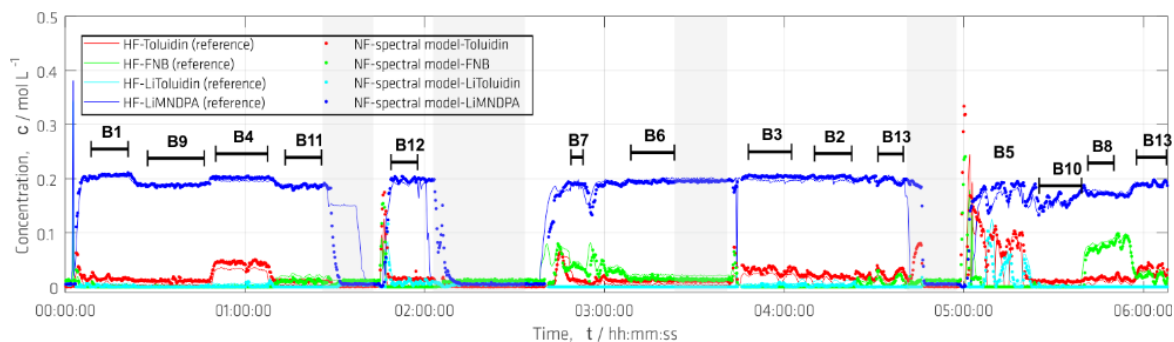


Figure 14. Amount of substance fractions observed with the LF NMR sensor of the reagents aniline and FNB and the product NDPA along an observation period of 6.5 hours together with HF NMR data. Grey areas represent points in time where pumps were not running due to cleaning or refilling.

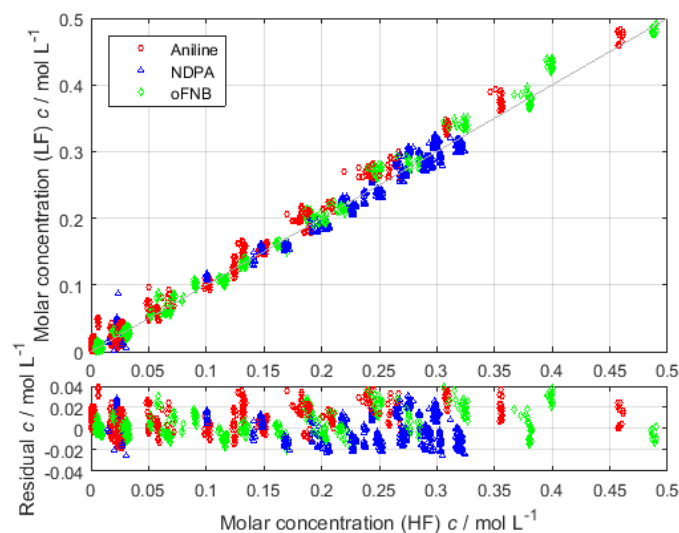


Figure 15. Parity plot of low-field (LF) versus high-field (HF) results in steady state during NDPA synthesis in batch mode. The grey line represents angle bisector and residuals represent deviations in mmol L^{-1} from the reference (HF).

The largest prediction uncertainties for IHM were found for aniline to be 5–7 % relative, i.e., 0.25–0.35 % absolute, or 20–30 mmol L^{-1} concentration deviation (as depicted in Fig. 15). As can be seen in Figure 12a, the signals of aniline completely overlap with the further reagents causing such model deviations. IHM slightly overestimates aniline in the low concentration range during equivalent fitting of the three pure component models, thus, underestimating the product NDPA. Minimizing the residues presents a closing condition for the fitting process. Improving IHM for these unwanted issues is currently undertaken [10].

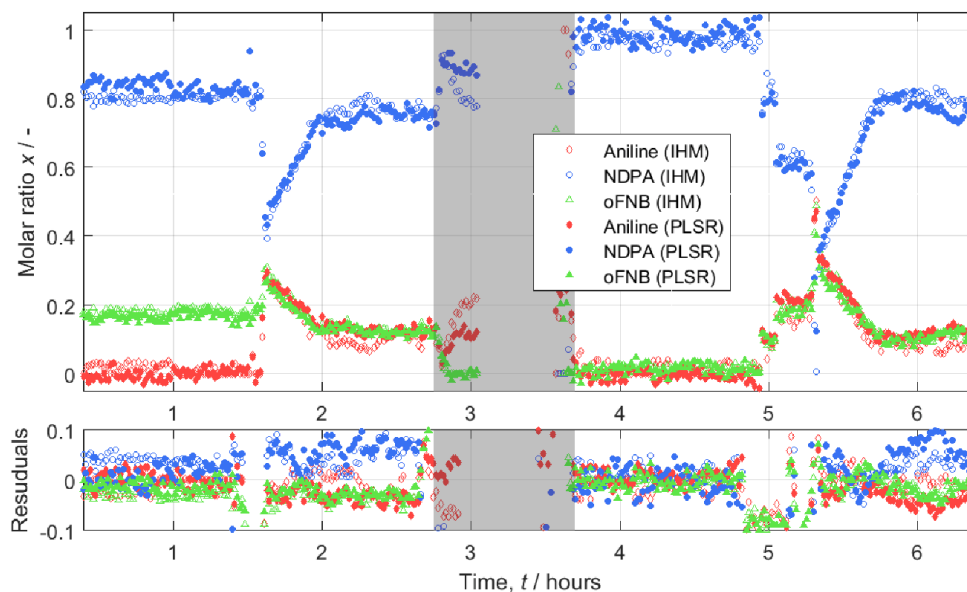


Figure 16. Prediction of continuous processes based on PLS-R and IHM models (external validation). To compare the predicted concentrations of Aniline, o-FNB and Li-NDPA with the reference data, ratios of the analytes summing up to 1 were calculated. Grey areas represent points in time where pumps were not running due to refilling of syringe pumps.

The online monitoring of continuous NDPA synthesis with low-field NMR spectroscopy was demonstrated in lab-scale for various process conditions. Due to major overlapping of signals in the aromatic region of the spectrum two multivariate models were applied – conventional PLS-R and IHM, based on spectral models – to quantify the reactants and products. Both methods yielded consistent results while comparing to the high-field NMR method even though based on completely different principles.

Whereas in the conventional PLS-R approach a set of three batch reactions were needed for model building (i.e., calibration), the same data sets were already used for both, building and validation of the IHM mixture model. In addition, a considerable number of continuous experiments were performed for validation taking account for various reaction conditions by individually adjusting the flow rates of the reagents aniline, o-FNB, and Li-HMDS. This data was used to verify the PLS-R model and to check the transferability of the IHM model.

Large product concentrations combined with a residual concentration of aniline below a few tens of mmol L^{-1} was found to be especially challenging for the data analysis due to almost complete overlapping of the spectral signals. As an implication uncertainties of one component induce further uncertainties in the remaining components since IHM is based on minimizing global residuals while deconvolution of the whole aromatic region of the spectrum into pure components. This fact explains the slightly higher RMSE values for aniline and Li-NDPA (i.e., 0.0182 and 0.0358) compared to PLS-R (i.e., 0.0247 and 0.0358) while RMSE values for FNB are comparable. It can be concluded, that IHM needs further constraints to find global minima in the mentioned challenging concentration regimes, which is a possible starting point for further improvement.

NMR specific information is currently not used for component fitting, e.g., if peaks get broader due to decreasing field homogeneity (deteriorate shimming) all peaks are affected in same manner. Consequently, this effect can be compensated by one parameter per pure component instead of fitting each peak width individually.

However, advantages of IHM include a minimum calibration effort (i.e., pure component spectra recorded in standard NMR tubes and one point calibration was sufficient) and high extrapolation capabilities, e.g., for

broader lines if shimming is an issue. Additionally, model adaption to new components such as byproducts, intermediates, or similar starting materials do not require complete new model development, in contrast, model constraints and common pure component models can be reused. For demonstration of this concept, the continuous set-up needs to be improved for high throughput facing low delay time and narrow residence time distribution and therefore fast gain of steady states.

2.4.2 Delivery and Installation of the NMR Sensor at INVITE

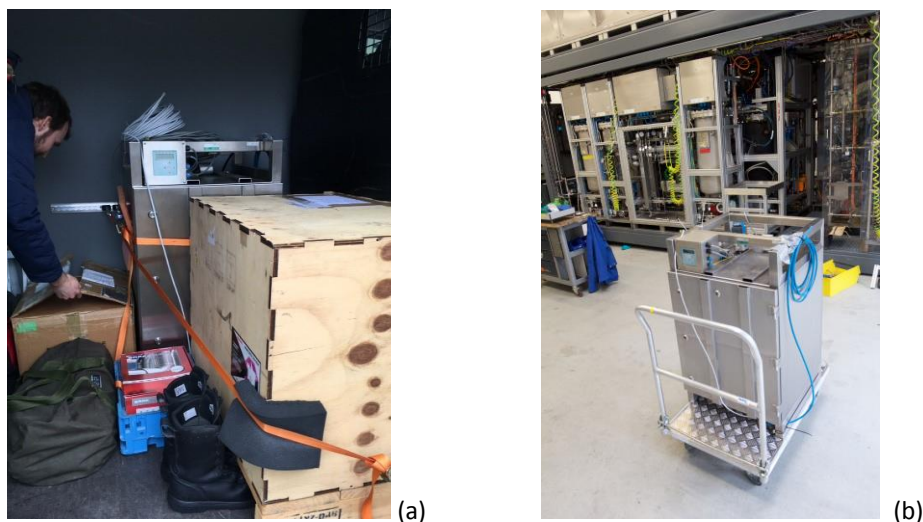


Figure 17. (a) Delivery of the pressurized enclosure on 21.03.2017 (Source: ABM); (b) Arrival of the box at INVITE, Leverkusen. CS1 modular production container in the background (Source: INVITE GmbH).



Figure 18. Arrival of the box at INVITE, Leverkusen. CS1 modular production container in the background. Group picture of BAM and INVITE team (Source: INVITE GmbH).

Finally, the pressurized enclosure was delivered in M27 to CS1 owner INVITE in Leverkusen on 21.03.2017.

2.4.3 First Test Runs of the NMR Sensor at INVITE

After integration of the NMR analyzer into the modular production plant at INVITE [12], first test runs were performed on 23.05.2017 and 06.06.2017. Figure 19 shows a typical diagram of the set-points for the pumps to vary the reactants with its explanations in Table 1.

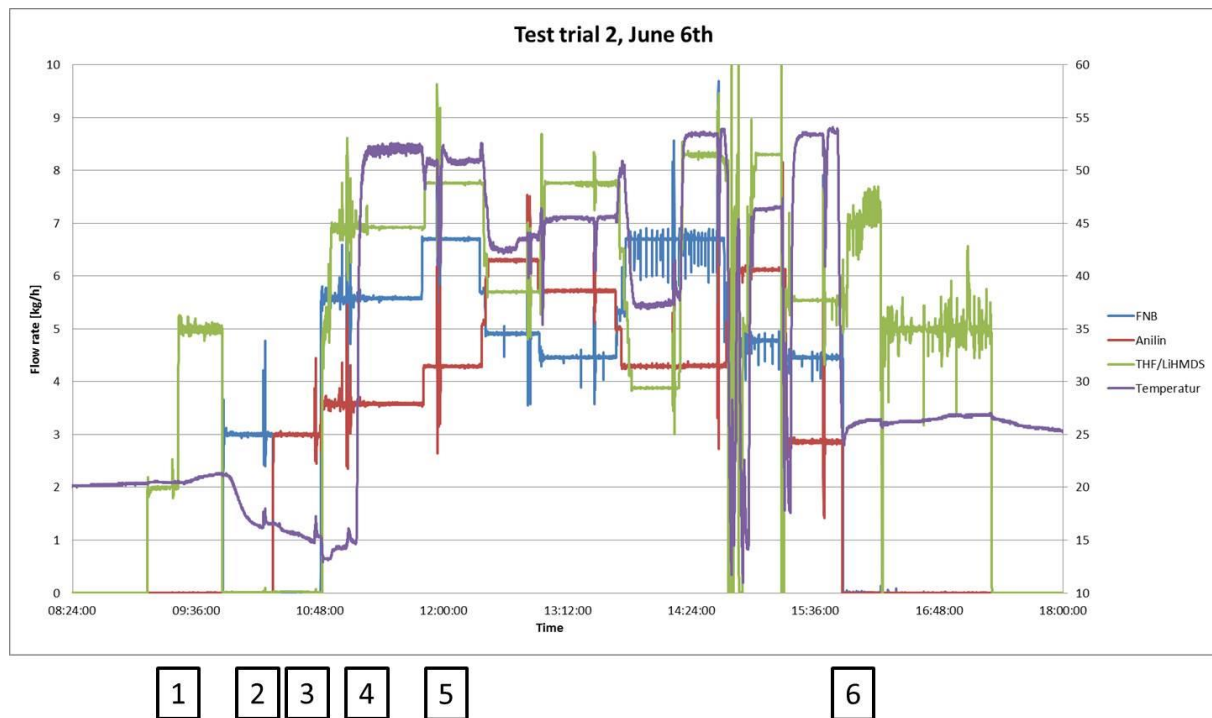


Figure 19. Diagram of the set-points for the pumps on 06.06.2017. Different experiments are explained in Table 1 below.

Table 1. Explanation of different experiments within one of the first test runs on 06.06.2017

Event	Explanation
1	Start feeding pure THF (Solvent) to ensure proper flow conditions for the bypass
2	Start feeding FNB solution to calibrate the NMR
3	Start feeding Aniline solution to calibrate the NMR
4	Start of the reaction, indicated by a steep increase in the temperature
5	Different step changes for a design of experiments (DoE) to train the control algorithm
6	Shut down of the reaction, cleaning with pure solvent

In the first test runs, the NMR sensor principally worked. However, the bypass system was not optimal at that time. Residence time distribution measurements by varying the analyzer feed revealed time delays in the order of 25 minutes, which had to be optimized for the subsequent runs by optimizing the filter and bypass section in the plant. To overcome this, the NMR sensor was programmed that the mass flow controller was set fully open to increase the mass flow as much as possible. It was only restricted to the critical quantitative mass flow for the analysis time (i.e., three NMR spectra were recorded in 15 s each). The results are depicted in Fig. 22b, which shows the alternatively switched mass flow in blue. However, this mode was not optimal due to increased danger of blocking of the NMR bypass by particles. This issue had also to be optimized for further runs by introducing a separate bypass line parallel to the NMR and inversely controlled bypass regulation by successive restriction of this bypass line.

The first test runs also exhibited a massive deviation of the experimentally recorded NMR spectra compared to the laboratory models (see Fig. 20a). It came out, that the stabilizer ethylbenzene was present to an extent of about 10 mass percent instead of the assumed ppm range. However, this issue was fixed by introducing an additional component for ethylbenzene to the IHM pure components (see Fig. 20b). In addition to that, a further component was added for lithiated aniline, which was also observed during the laboratory experiments. Lithiated aniline is present, when a considerable excess of Li-HMDS was added to the reaction mixture. It represents a “speciation” of aniline, which is only present in the reaction mixture under process conditions. Such components could not be observed after sampling and subsequent quenching of the sample (and hence not observable by HPLC reference analytics). This is one of the important result of the experiments in CS1, since online NMR analyzer makes such species accessible.

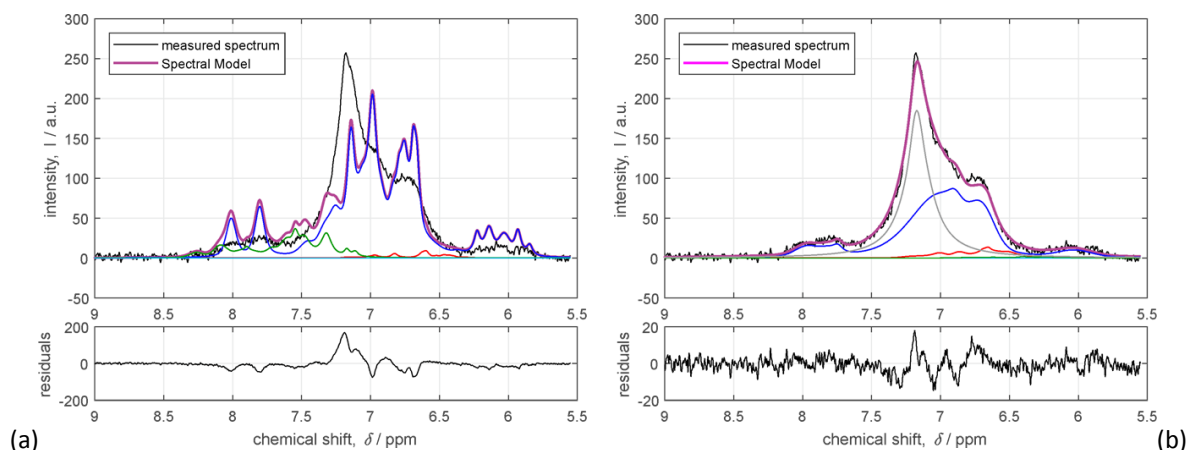


Figure 20. Model output of the IHM calculation (pink: Spectral model) compared to the measured spectrum (black) together with individual pure component models (red, green, and blue). (a) left figure exhibits large residuals due to imperfect fit of the IHM model. The reason is an additional pure component ethylbenzene; (b) ethylbenzene was successfully added as an additional pure component in the IHM model.

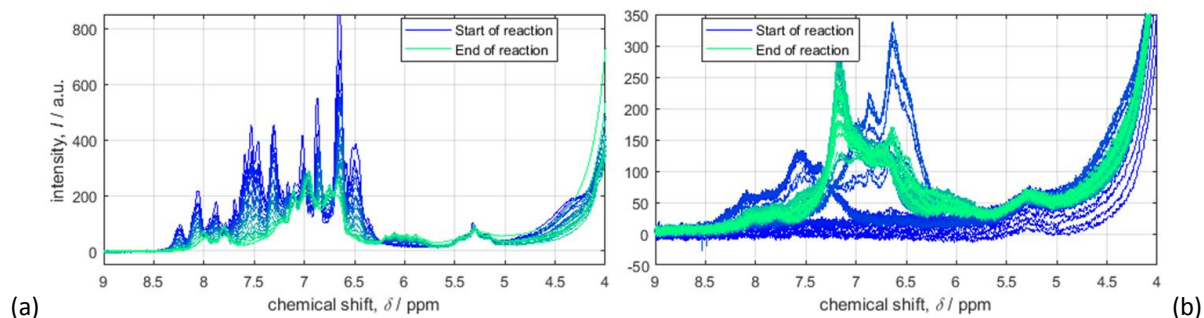


Figure 21. Imperfections of the experimental spectra acquired in the plant (b, right) compared to the laboratory spectra (a, left, see also Fig. 10b). These imperfections are due to insufficient shimming of the instrument due to imperfect thermostating at this run.

However, despite the poor spectral quality of the experimental online NMR spectra due to insufficient shimming of the instrument, which were the result of imperfect thermostating at this run, and the rough adaption of the IHM model by addition of the ethylbenzene pure component, the final results of the NMR sensor were very reasonable as depicted in Figure 22a. In this figure the molar concentrations of five different species along the continuous run of the modular plant are depicted.

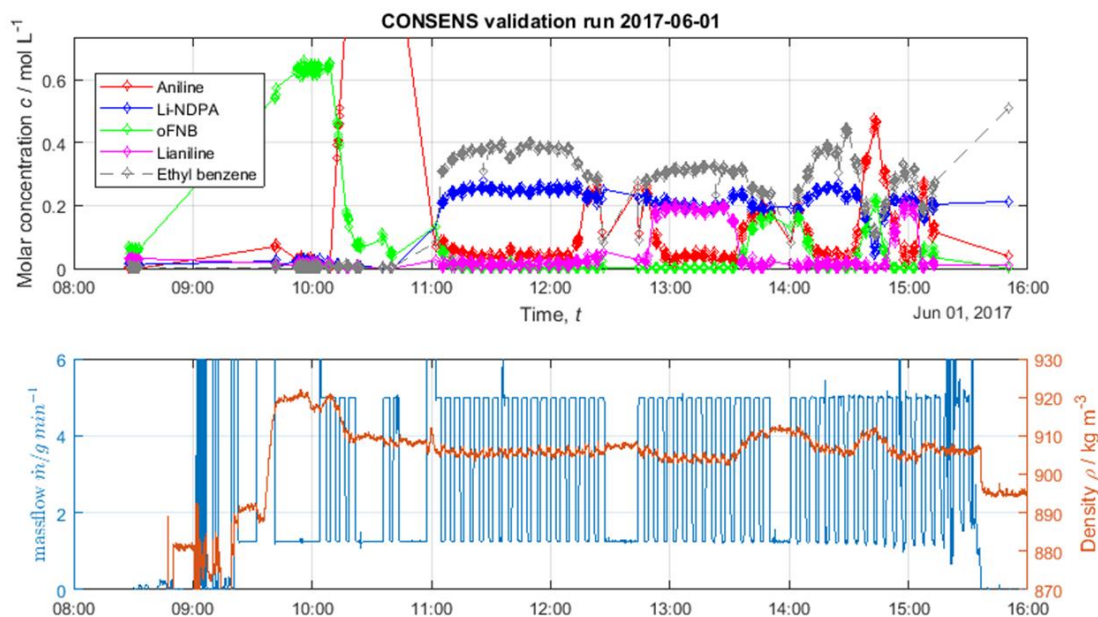


Figure 22. (a, top) Molar concentrations of the five different species aniline (red), Li-NDPA (blue), oFNB (green), the lithiated aniline (pink) and the “stabilizer” ethylbenzene (grey), which was found in the reagent Li-HMDS along the continuous run of the modular plant. (b, bottom) depicts mass flows (blue), which were switched between maximum mass flow and quantitative mass flow to decrease the response times for that experiment and densities (orange).

Despite the abovementioned issues, the first two test trials show a steep learning curve for all partners and the ideas for improvements shows that there was plenty of room for potential.

2.4.4 Improvement of the NMR Sensor

As an outcome of the first validation runs, all partners improved their systems. Main improvements of the NMR sensor were improvement of the IHM models for all involved species (as mentioned above), improvement of the NMR flow cell, and improvement of the sample loop within the NMR analyzer.

The latter is schematically shown in Figure 23. As described above (see Fig. 2 in Section 2.2.1) the initial sample bypass is directly regulated by a closing regulation valve attached to the mass flow controller. The maximum diameter of the opened valve was only 0.15 mm, which was causing blockages of the NMR sensor.

In the new concept (Fig. 23b) the introduced bypass section allows for a maximum flow rate of up to 10 mL min^{-1} . The optimal quantitative mass flow through the NMR flow cell is inversely regulated by an opening regulation valve with a diameter of 1.3 mm in the bypass section. This tremendously reduces the danger of blocking of the NMR analyzer by particles and increases the maximal mass flow at the same time while decreasing the response time of the sensor.

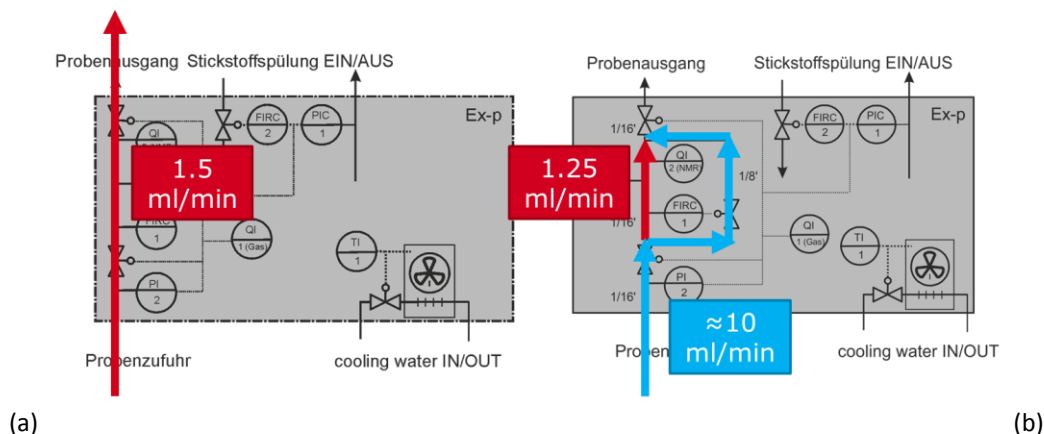


Figure 23. (a) first prototype of the sample bypass of the online NMR analyzer (see Fig. 2 in Section 2.2.1). Here the sample bypass is directly regulated by a closing regulation valve attached to the mass flow controller. (b) schematically depicts the introduced bypass section, which allows for a maximum flow rate of up to 10 mL min⁻¹. The optimal quantitative mass flow through the NMR flow cell (red) is inversely regulated by an opening regulation valve in the bypass section. (Probenzufuhr = sample inlet, Probenausgang = sample outlet).

2.4.5 Final Test Runs of the NMR Sensor at INVITE

After the abovementioned improvements of the online NMR analyzer together with improvements at INVITE [12] several further test runs were performed on 26.09.2017 (8.5 hours), 28.09.2017 (6.5 hours), and 10.10.2017 (12.5 hours). The details of these test runs along with the original experimental data will be presented in near future in further details (see publications on www.consens-spire.eu). The following figures show only representative results.

In the trial from 26.09.2017 (see Fig. 24 below) at first the raw material solutions were fed without additional dilution by the solvent stream. Also pure LiHMDS was fed, which is indicated indirectly by the stabilizer ethyl benzene. The whole procedure from starting with oFNB first until the start of the reaction at 12:15 is quite long (2:30 hours), but mandatory to characterize the time delay in the by-pass and also to achieve stable conditions of the raw materials. In this test trial the conditions for the step changes in the raw material solutions was tested at the beginning. The start flow rates was oFNB: 5.6 kg h⁻¹, aniline: 3.68 kg h⁻¹, and LiHMDS: 6.89 kg h⁻¹, respectively. The first increase of oFNB after the start of the reaction does not lead to higher concentration of the FNB in the NMR measurement.

The details of the test run presented in Figure 24 is not the focus of this report and presented elsewhere (see publications on www.consens-spire.eu). However, the online NMR sensor gave reasonable and stable results over all courses of the reaction. The response times, which were again derived from the step change experiments at the beginning, were in the order of 3–7 min. Short-time stabilities of the acquired concentrations (including stabilities if the pumps, NMR data acquisition, and IHM calculations) are roughly in the order of 10 mmol L⁻¹, which is an extraordinarily respectable result.

However, slight overestimations of low concentrated species such as the reagents aniline and oFNB were observed, which are roughly below 10–20 mmol L⁻¹, as can be seen in Fig. 25. These results are currently still under investigation.

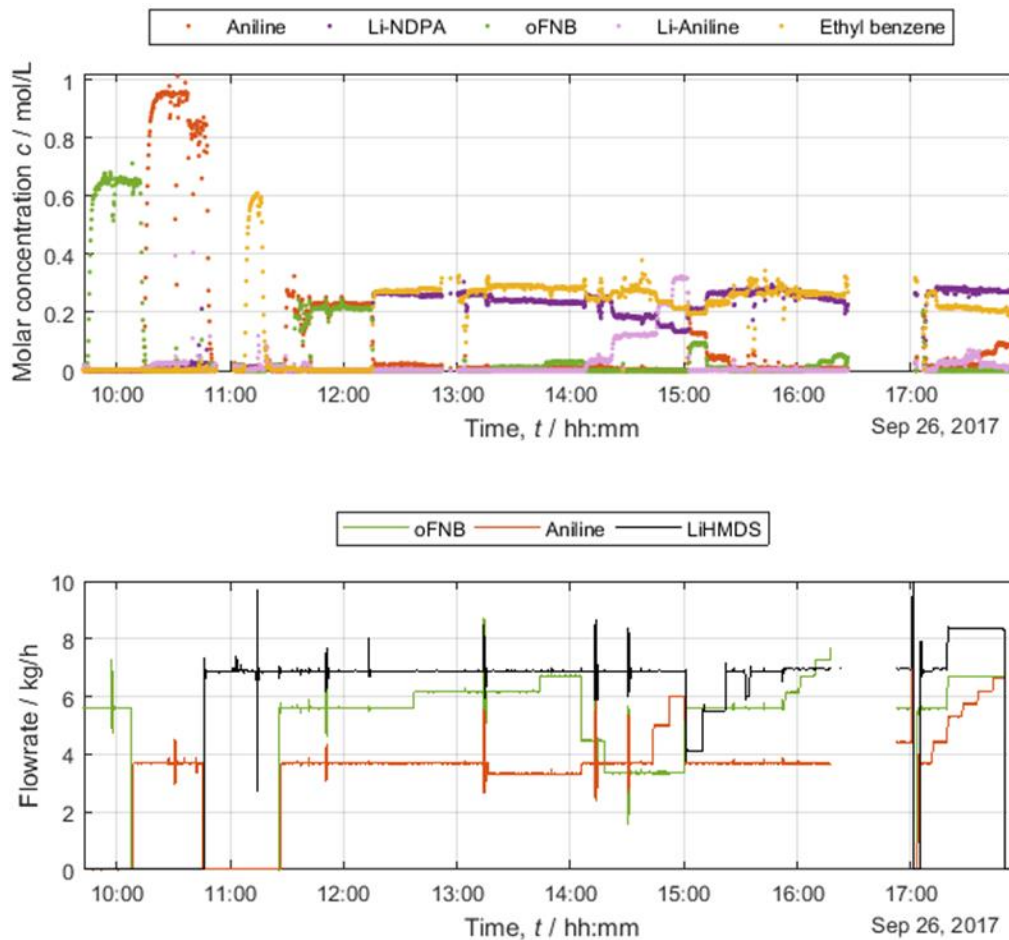


Figure 24. (a, top) Molar concentrations of the five different species aniline (red), Li-NDPA (blue), oFNB (green), the lithiated aniline (pink) and the “stabilizer” ethylbenzene (orange) along the continuous run of the modular plant on 26.09.2017 at INVITE [12]. (b, bottom) depicts mass flows of the three reagents oFNB (green), aniline (red), and Li-HMDS (black).

Figure 25 shows a more detailed excerpt of some molar concentrations of the five different species aniline, Li-NDPA, oFNB, lithiated aniline, and ethylbenzene. This figure shows a time offset of about 3 minutes between change of the set-points of the pumps as well as the approach of the steady state concentrations as a steep change to the new concentration with only short time delays (e.g., for aniline (orange) at 10:05 in Fig. 25a).

The figure also exhibits some long and short term oscillations in the Li-HMDS pump (see black curve in Fig. 25b). Accordingly, the reaction is influenced by this oscillating concentration changes leading to oscillating concentrations of all reagents and the reaction product Li-NDPA in Figure 25a, which is again a particularly respectable result for the time behavior of the NMR analyzer.

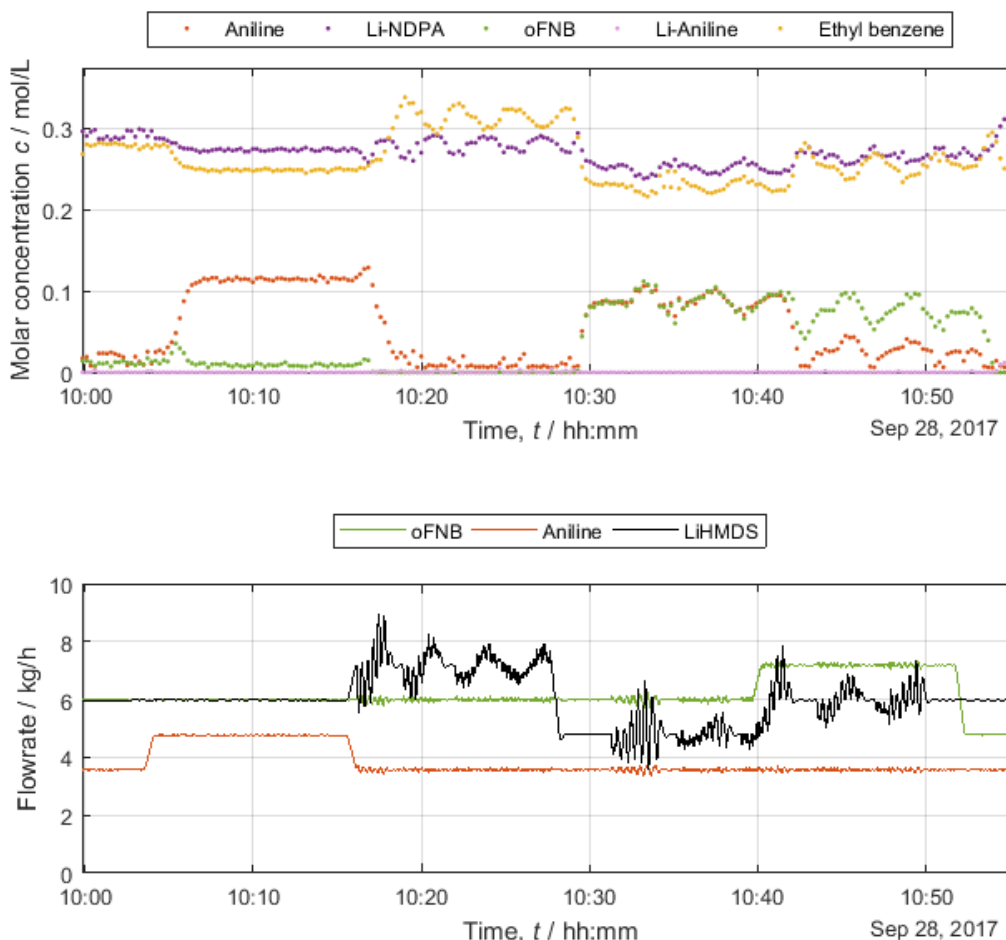


Figure 25. (a, top) More detailed excerpt of some molar concentrations of the five different species aniline (red), Li-NDPA (blue), oFNB (green), the lithiated aniline (pink) and the “stabilizer” ethylbenzene (orange) along the continuous run of the modular plant on 28.09.2017 at INVITE [12]. (b, bottom) depicts mass flows of the three reagents oFNB (green), aniline (red), and Li-HMDS (black).

2.5 Conclusion and Outlook

Monitoring specific chemical properties is the key to chemical process control. Today, mainly optical online methods are applied, which require excessive calibration effort. It was shown that NMR spectroscopy, with its advantage being a direct comparison method without need for calibration, has a high potential for direct loop process control while exhibiting short set-up times. Compact NMR instruments make NMR spectroscopy accessible in industrial and rough environments for process monitoring and advanced process control strategies.

We developed and validated a fully automated data analysis approach which is completely based on physically motivated spectral models as first principles information (Indirect Hard Modelling – IHM) and applied it to a given pharmaceutical lithiation reaction in the framework of the European Union’s Horizon 2020 project CONSENS. Online low-field NMR data was analysed by IHM with extremely low calibration effort, compared to a multivariate PLS-R (Partial Least Squares Regression) approach, and both validated using online high-field NMR spectroscopy. Based on pure component spectra, derived from preliminary test reactions and measured in standard NMR tubes, quantitative results were already achieved using the Indirect Hard Modeling approach. This means, that for online NMR spectra, area to concentration conversion, i.e., a one-point-calibration throughout initial concentrations of o-FNB was performed and used for all further data analysis.

Succeeding, for external validation of this method spectra from the continuous process were evaluated as shown above in Figure 16. Here, molar ratios were calculated without prior calibration based on normalized (i.e., considering proton numbers per reactant) peak area ratios due to the lack of calibration data. Figure 16 indicates similar results for online NMR data evaluation with the NMR analyzer compared to high-field (500 MHz) NMR spectroscopy as the reference method.

However, when aniline is not present the predictions of IHM show a biased deviation in between 0–20 mmol L⁻¹. This is presumably due to the applied component fitting algorithm, when aniline is deployed by the IHM model even though it is not present while minimizing the global residues upon spectral noise while allowing flexibility of the pure component models. Such an over-estimation by IHM was only found for aniline, which aromatic NMR signals completely fall together with other components. In contrary, small area fractions, which belong to NDPA are erroneously represented by the aniline model. For aniline, this effect was observed below concentrations below 20 mmol L⁻¹ whereas for o-FNB it was never problematic.

Despite the abovementioned shortcomings for slight over-estimations of the component aniline the developed online NMR sensor was successfully validated against reference methods in the laboratory as well as in several test runs in the industrial environment with extremely short time behavior. Also, the short-time stabilities of the acquired concentrations in the order of 10 mmol L⁻¹ were extraordinarily respectable results.

3 Appendix

3.1 Bibliography

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3.2 Acknowledgements

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3.3 CONSENS Publications and Presentations of BAM

Book Chapter

- Michael Maiwald, „Prozess-Sensoren 4.0“ – Chancen für neue Automatisierungskonzepte und neue Geschäftsmodelle in der Prozessindustrie, in „Safety and Security – Mit Sicherheit gut vernetzt“, V. Becker, C. Pinnow, S. in „Industrie 4.0 - Safety and Security - Mit Sicherheit gut vernetzt - Branchentreff der Berliner und Brandenburger Wissenschaft und Industrie“, Carsten J. Pinnow, Stephan Schäfer (Eds.), Beuth-Verlag, Berlin, 2017, S. 135–150 – ISBN: 978-3-410-26406-4;
URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-434368>

Peer Reviewed Papers

- Simon Kern, Aleksandra Michalik-Onichimowska, Jens Riedel, Ulrich Panne, Rudibert King, Michael Maiwald, “Click” analytics for “click” chemistry – a simple method for calibration-free evaluation of online NMR spectra, *Journal of Magnetic Resonance* 277 (2017) 154–161; <http://dx.doi.org/10.1016/j.jmr.2017.02.018>
URL: <http://www.sciencedirect.com/science/article/pii/S1090780717300575>
DOI: <http://dx.doi.org/10.1016/j.jmr.2017.02.018>
- Klas Meyer, Simon Kern, Nicolai Zientek, Gisela Guthausen, Michael Maiwald, Process control with compact NMR, *Trends in Analytical Chemistry* 83 (2015) 39–52 (Review), <http://dx.doi.org/10.1016/j.trac.2016.03.016> (Green Open Access in March 2018)
URL: <http://www.sciencedirect.com/science/article/pii/S0165993616300073>
DOI: <http://dx.doi.org/10.1016/j.trac.2016.03.016>
- Simon Kern, Klas Meyer, Svetlana Guhl, Patrick Gräßer, Rudibert King, Andrea Paul, Michael Maiwald, Online Low-Field NMR Spectroscopy for Process Control of an Industrial Lithiation Reaction – Automated Data Analysis (submitted)

Papers

- Simon Kern, Klas Meyer, Michael Maiwald: „NMR-Spektroskopie im Feld – Eine neue Online-Methode für die Prozesskontrolle“, ATP-Edition 2016(12), 21–25
URL: <https://opus4.kobv.de/opus4-bam/frontdoor/index/index/docId/38675>

Research Reports

- Simon Kern, Svetlana Guhl, Klas Meyer, Michael Maiwald: “Validation report on NMR” (D1.9)
URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-435521>

Proceedings

- 11. Kolloquium Prozessanalytik, Wien, Austria, 30.11.–02.12.2015
- **Simon Kern**, Patrick Gräßer, Nicolai Zientek, Michael Maiwald: „First steps towards field integration of benchtop NMR spectroscopy for online monitoring and process control” (Conference Proceeding)
URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-388411>

ProcessNet-Jahrestagung und 32. DECHEMA-Jahrestagung der Biotechnologen, Aachen, Germany, 12.–15.09.2016

- Simon Kern, Klas Meyer, Andrea Paul, Michael Maiwald: „Ugly spectra and lousy interfaces – Challenges for compact NMR spectroscopy in process control”, *Chem. Ing. Tech.* 88 (2016) 1312–1313 (Conference Proceeding)
URL: <http://onlinelibrary.wiley.com/doi/10.1002/cite.201650243/full>
DOI: <http://dx.doi.org/10.1002/cite.201650243>

12. Kolloquium AK Prozessanalytik, 28.–30.12.2016, Berlin

- **Svetlana Guhl**, Klas Meyer, Simon Kern, Patrick Gräßer, Michael Maiwald: “Process Monitoring of an Intensified Continuous Production Unit with Compact NMR Spectroscopy” (Proceeding)
URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-383646>

11. Interdisziplinäres Doktorandenseminar Berlin, 12.–14.03.2017

- **Simon Kern**, Aleksandra Michalik-Onichimowska, Jens Riedel, Ulrich Panne, Rudibert King, Michael Maiwald: ““Click” analytics for “click” chemistry – a simple method for calibration-free evaluation of online NMR spectra”, *Proceedings*, 33–35 (Proceeding)
URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-435531>

Euroensors XXXI 2017, 03.–06.09.2017, Paris, France

- Michael Maiwald, Patrick Gräßer, Lukas Wander, Nicolai Zientek, Svetlana Guhl, Klas Meyer, Simon Kern: „Strangers in the Night – Smart Process Sensors in Our Current Automation Landscape” (Conference Proceeding, BAM_2017_19), *Proceedings* 2017, 1, 628; doi:10.3390/proceedings1040628
URL: <http://www.mdpi.com/2504-3900/1/4/628>
URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-415772>
DOI: <http://dx.doi.org/10.3390/proceedings1040628>

International Conference Advanced Mathematical and Computational Tools in Metrology and Testing XI (AMCTM 2017), 29.–31.08.2017 University of Strathclyde, Glasgow, Scotland

- Simon Kern, Svetlana Guhl, Klas Meyer, Andrea Paul, Wolfram Bremser, and Michael Maiwald: “Mathematical and statistical tools for online NMR spectroscopy in chemical processes” (Full Paper AMCTM Book, in print)

Dresdner Sensor Symposium, 4.–6.12.2017, Dresden, Germany

- Michael Maiwald, Patrick Gräßer, Lukas Wander, Svetlana Guhl, Klas Meyer, Simon Kern: „Innen hui und außen pfui – Smarte Prozess-Sensoren in der gegenwärtigen Automatisierungslandschaft der Prozessindustrie“, *Tagungsband 13. Dresdner Sensor-Symposium, AMA*, 61–66 – DOI 10.5162/13dss2017/2.1 (Full Paper) – ISBN 978-3-9816876-5-1
URL: <https://www.ama-science.org/proceedings/details/2717>
DOI: <http://dx.doi.org/10.5162/13dss2017/2.1>

- Simon Kern, Svetlana Guhl, Klas Meyer, Andrea Paul, and Michael Maiwald: „Mathematical and statistical tools for online NMR spectroscopy in chemical processes” *Tagungsband 13. Dresdner Sensor-Symposium, AMA*, 209–212 – DOI 10.5162/13dss2017/P2.07 (Full Paper) – ISBN 978-3-9816876-5-1
URL: <https://www.ama-science.org/proceedings/details/2748>
DOI: <http://dx.doi.org/10.5162/13dss2017/P2.07>

Posters and Presentations

INVITE Colloquium, Leverkusen, Germany, 08.09.2015

- **Michael Maiwald**, Nicolai Zientek, Klas Meyer, Simon Kern: “Low field NMR Spectroscopy for online monitoring” (Talk)
URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-361417>

SMASH (Small Molecules NMR Conference), Baveno, Italy, 17.–22.09.2015

- Michael Maiwald, Nicolai Zientek, Klas Meyer, Andrea Paul, Dirk Engel, Matthias Kraume, Gisela Guthausen: “Automated Data Evaluation and Modeling of Simultaneous ¹⁹F-¹H Benchtop NMR Spectra for Online Reaction Monitoring” (Talk)
URN <http://nbn-resolving.org/urn:nbn:de:kobv:b43-351645>
- **Simon Kern**, Nicolai Zientek, Michael Maiwald: „First steps towards field integration of benchtop NMR spectroscopy for online

monitoring and process control" (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-351085>

11. Kolloquium Prozessanalytik, Wien, Austria, 30.11.–02.12.2015

• **Simon Kern**, Patrick Gräßer, Nicolai Zientek, Michael Maiwald: „First steps towards field integration of benchtop NMR spectroscopy for online monitoring and process control" (Poster)

URL: <https://opus4.kobv.de/opus4-bam/frontdoor/index/index/docId/35159>

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-351597>

Pro2NMR Autumn School, 08.12.2015, Aachen, Germany

• **Simon Kern**, Patrick Gräßer, Nicolai Zientek, Michael Maiwald: „First steps towards field integration of benchtop NMR spectroscopy for online monitoring and process control" (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-351097>

4th Process Applications of NMR in Industry Conference (PANIC 2016), 16.–19.02.2016, Houston, TX, USA

• **Simon Kern**, Patrick Gräßer, **Klas Meyer**, Nicolai Zientek, Andrea Paul, Michael Maiwald: "Field integration of benchtop NMR instruments for online monitoring and process control of a modular industrial reaction step" (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-354427>

2nd Poster Prize

10. Interdisziplinäres Doktorandenseminar, Berlin, Germany, 28.02.2016

• **Simon Kern**, **Klas Meyer**, Andrea Paul, Michael Maiwald: "Online low-field NMR spectroscopy of an industrial lithiation reaction step for process control" (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-354443>

ProcessNet-Jahrestagung und 32. DECHEMA-Jahrestagung der Biotechnologen, Aachen, Germany, 12.–15.09.2016

• **Simon Kern**, **Klas Meyer**, Andrea Paul, Michael Maiwald: „Ugly spectra and lousy interfaces – Challenges for compact NMR spectroscopy in process control" (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-373895>

12. Kolloquium AK Prozessanalytik, 28.–30.12.2016, Berlin

• **Svetlana Guhl**, **Klas Meyer**, **Simon Kern**, Patrick Gräßer, Michael Maiwald: "Process Monitoring of an Intensified Continuous Production Unit with Compact NMR Spectroscopy" (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-385628>

1. Forum Embedded Spektroskopie, Adlershof Berlin, Germany, 01.12.2016

• Michael Maiwald: „Die Technologie-Roadmap „Prozess Sensoren 4.0" - Chancen für neue Automatisierungskonzepte und neue Geschäftsmodelle" (Invited Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-385611>

NMR-Diskussionstagung Praktische Probleme der Kernresonanzspektroskopie, Erlangen, Germany, 16.–17.01.2017

• **Simon Kern**, **Klas Meyer**, Lukas Wander, Svetlana Guhl, Andrea Paul, Michael Maiwald: "Online-Niederfeld-NMR-Spektroskopie in modularen Anlagen der Prozessindustrie" (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-389819>

Quantitative NMR Methods for Reaction and Process Monitoring – NMRPM, Symposium, 19.–20.01.2017, Kaiserslautern, Germany

• **Michael Maiwald**, **Klas Meyer**, **Simon Kern**, Svetlana Guhl, Patrick Gräßer, Lukas Wander, Andrea Paul: "Man proposes, God disposes – The way from reaction monitoring to industrial automation" (Invited Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-389940>

• **Svetlana Guhl**, **Simon Kern**, **Klas Meyer**, Lukas Wander, Patrick Gräßer, Michael Maiwald: „Design and validation of a compact NMR analyser" (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-390117>

CONSENS Public Workshop for Process Industry "Tackling the Future of Plant Operation", 25.01.2017, Dechema, Frankfurt

• **Svetlana Guhl**, **Klas Meyer**, **Simon Kern**, Patrick Gräßer, Michael Maiwald: "Process Monitoring of an Intensified Continuous Production Unit with Compact NMR Spectroscopy" (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-391386>

5th Process Applications of NMR in Industry Conference (PANIC 2017), 20.–23.02.2017, Hilton Head Island, SC, USA

• **Simon Kern**, **Klas Meyer**, Svetlana Guhl, Patrick Gräßer, Lukas Wander, Andrea Paul, Michael Maiwald: "Low Field NMR Spectroscopy for Sustainable and Flexible Production of High Quality Chemical Products" (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-392333>

11. Interdisziplinäres Doktorandenseminar, Berlin, 12.–14.03.2017

• **Svetlana Guhl**, **Simon Kern**, **Klas Meyer**, Patrick Gräßer, Lukas Wander, Michael Maiwald: „Online Niederfeld-NMR-Spektroskopie in modularen Anlagen der Prozessindustrie" (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-394241>

qNMR-Summit, Symposium on Quantitative NMR Spectroscopy, 16.–17.03.2017, BAM, Berlin, Germany

• **Klas Meyer**, **Simon Kern**, Michael Maiwald: "Workshop I: Automated Data Preparation and Spectral Modeling" (60 min Workshop with Talk and live data analysis session)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-393998>

Royal Society of Chemistry NMR and MolSpec Discussion Groups "Low level detection and quantification by NMR", Stevenage, United Kingdom, 29.03.2017

• **Michael Maiwald**, Claudia Peters, **Klas Meyer**, **Simon Kern**, Svetlana Guhl, Patrick Gräßer, Lukas Wander: „How Far does the Light Shine? – A Check-Up of Quantitative High and Low Field NMR Spectroscopy" (Invited Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-395936>

ANAKON 2017 (Analytical Conference), Tübingen, Germany, 03.–06.04.2017

• **Svetlana Guhl**, **Simon Kern**, **Klas Meyer**, Lukas Wander, Patrick Gräßer, Michael Maiwald: „Design and validation of a compact NMR analyser" (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-396960>

Tagung Industrie 4.0 - "Safety und Security – Mit Sicherheit gut vernetzt", Hochschule für Technik und Wirtschaft Berlin, Berlin, 28.04.2017

• Michael Maiwald: „„Prozess-Sensoren 4.0" – Chancen für neue Automatisierungskonzepte und neue Geschäftsmodelle in der Prozessindustrie" (Invited Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-400262>

EuroPACT 2017, 10.–12.05.2017, Potsdam, Germany

• **Simon Kern**, Svetlana Guhl, **Klas Meyer**, Andrea Paul, Lukas Wander, Patrick Gräßer, Michael Maiwald: "Design and Validation of a Compact NMR Analyser" (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-402822>

• **Svetlana Guhl**, **Simon Kern**, **Klas Meyer**, Lukas Wander, Patrick Gräßer, Michael Maiwald: "Online NMR Spectroscopy for Process Monitoring in Intensified Continuous Production Plants" (Poster)

• URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-435507>

EuroSensors XXXI 2017, 03.–06.09.2017, Paris, France

• **Michael Maiwald**, Patrick Gräßer, Lukas Wander, Nicolai Zientek, Svetlana Guhl, **Klas Meyer**, and **Simon Kern**: "Strangers in the Night – Smart Process Sensors in Our Current Automation Landscape" (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-418271>

Pharma Talk Berlin 2017, Berlin, Germany, 08.–09.06.2017

- **Michael Maiwald**: “Using Smart Sensors and Modular Production Units for Sustainable and Flexible Production of High Quality Chemicals and Pharmaceuticals” (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-405039>

Institutseminar, Institut für Mathematik Universität Rostock, Rostock, Germany, 12.07.2017

- **Simon Kern, Michael Maiwald**: „Low field NMR spectroscopy for process control - robust automated data preparation and analysis as prerequisites“ (Invited Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-409694>

Swiss Chemical Society Fall Meeting, Symposium on PAT & Industry 4.0, University of Bern, Bern, Switzerland, 21.–22.08.2017

- **Michael Maiwald, Patrick Gräßer, Lukas Wander, Svetlana Guhl, Klas Meyer, Simon Kern**: “Sensor Roadmap 4.0 – Prospects towards a uniform topology for process control and smart sensor networks” (Invited Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-414683>

International Conference Advanced Mathematical and Computational Tools in Metrology and Testing XI (AMCTM 2017), 29.–31.08.2017 University of Strathclyde, Glasgow, Scotland

- **Simon Kern, Svetlana Guhl, Klas Meyer, Andrea Paul, Wolfram Bremser, and Michael Maiwald**: “Mathematical and statistical tools for online NMR spectroscopy in chemical processes” (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-416560>

SMASH (Small Molecules NMR Conference), Baveno, Italy, 17.–22.09.2017

- **Simon Kern, Klas Meyer, Svetlana Guhl, Andrea Paul, Michael Maiwald**: “Design and Validation of a compact online NMR module” (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-419473>

- **Lukas Wander, Simon Kern, Klas Meyer, Svetlana Guhl, Michael Maiwald**: “Assessment and Validation of Various Flow Cell Designs for Quantitative Online NMR Spectroscopy” (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-419485>

- **Simon Kern, Svetlana Guhl, Klas Meyer, Andrea Paul, Michael Maiwald**: “Reading between the lines – automated data analysis for low field NMR spectra” (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-419498>

13. Kolloquium des Arbeitskreises Prozessanalytik, Esslingen, Germany, 20.–22.11.2017

- **Svetlana Guhl, Klas Meyer, Simon Kern, Patrick Gräßer, Lukas Wander, Jörg Acker, Michael Maiwald**: „Prozessen auf der Spur mit Online-NMR-Spektroskopie – Eine Chance für Industrie 4.0 in der Prozessindustrie“ (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-431096>

- **Simon Kern, Svetlana Guhl, Lukas Wander, Klas Meyer, Michael Maiwald**, “Simple Calibration Concept of an Online NMR Module

Demonstrated in a Modularised Production Plant (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-430999>

- **Lukas Wander, Simon Kern, Svetlana Guhl, Klas Meyer, Michael Maiwald**: „Keramikdurchflusszellen für das industrielle Prozessmonitoring mit Niederfeld-NMR-Spektroskopie“ (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-430918>

Dresdner Sensor Symposium, 4.–6.12.2017, Dresden, Germany

- **Michael Maiwald, Patrick Gräßer, Lukas Wander, Svetlana Guhl, Klas Meyer, Simon Kern**: „Innen hui und außen pfui – Smarte Prozess-Sensoren in der gegenwärtigen Automatisierungslandschaft der Prozessindustrie“ (Invited Keynote Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-432056>

- **Simon Kern, Svetlana Guhl, Klas Meyer, Andrea Paul, Michael Maiwald**: „Mathematical and statistical tools for online NMR spectroscopy in chemical processes” (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-432085>

Workshop “Tackling the Future of Plant Operation – Jointly towards a Digital Process Industry” Barcelona, Spain, 13.–14.12.2017

- **Michael Maiwald, Simon Kern, Klas Meyer, Svetlana Guhl, Lukas Wander, Andrea Paul**: “Already Producing or Still Calibrating? – Online NMR Spectroscopy as Smart Field Device.” (Talk)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-434330>

- **Lukas Wander, Simon Kern, Klas Meyer, Svetlana Guhl, Andrea Paul, Michael Maiwald**: “Design and Validation of a compact online NMR module” (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-434346>

- **Svetlana Guhl, Simon Kern, Klas Meyer, Andrea Paul, and Michael Maiwald**: “Reading Between the Lines – Automated data analysis for low field NMR spectra” (Poster)

URN: <http://nbn-resolving.org/urn:nbn:de:kobv:b43-434351>

Upcoming

6th Process Applications of NMR in Industry Conference (PANIC 2018), 04.–08.03.2018, LaJolla, CA, USA

- **Michael Maiwald, Simon Kern, Svetlana Guhl, Klas Meyer, Lukas Wander, Andrea Paul**: “Already Producing or Still Calibrating? – Advances of Model-Based Data Evaluation Concepts for Quantitative Online NMR Spectroscopy” (accepted Poster)

- **Simon Kern, Martin Bornemann, Lukas Wander, Klas Meyer, Svetlana Guhl, Michael Maiwald**: “Novel flow cell designs for process monitoring with compact NMR spectroscopy” (accepted Poster)

- **Svetlana Guhl, Klas Meyer, Simon Kern, Patrick Gräßer, Lukas Wander, Jörg Acker, Michael Maiwald**: “Process Monitoring with Online NMR Spectroscopy – An Enabler for “Industrie 4.0” in Process Industry” (accepted Poster)