Calibration-Free Chemical Process and Quality Control Units as Enablers for Modular Production

Martin Bornemann-Pfeiffer[1,2], Simon Kern[1,3], Michael Maiwald[1,*], and Klas Meyer[1]

DOI: 10.1002/cite.202000150

Dedicated to Prof. Dr.-Ing. Matthias Kraume on the occasion of his 65th birthday

Modular chemical production is a tangible translation of the digital transformation of the process industry for specialty chemicals. In particular, it enables the speeding-up of process development and, thus, a quicker time to market by flexibly connecting and orchestrating standardized physical modules and bringing them to life (i.e., parameterizing them) with digitally accumulated process knowledge. We focus on the specific challenges of chemical process and quality control, which in its current form is not well suited for modular production and provide possible approaches and examples of the change towards direct analytical methods, analytical model transfer or machine-supported processes.

Keywords: Chemical process control, Digital transformation, Modular production, Process analytical technology

Received: July 16, 2020; *revised:* October 19, 2020; *accepted:* November 13, 2020

1 Introduction

As early as the 1970s, there are approaches that propagate a shortened market introduction of chemicals and pharmaceuticals, e.g., by skipping scale-up steps in process development [1]. The vision of that time has proven to be extremely valuable, especially in the production of specialty chemicals. European companies in the process industry are increasingly pushing into the market for specialty chemicals in order to benefit from the higher profit margins in this sector. The complexity of the sector could prove to be an advantage for Europe and could benefit from the technical know-how of local producers. More recently, the approaches have been systematically taken up, including in particular the "50 % idea", which was born at the Tutzing Symposion 2009 more than ten years ago [1, 2]. This concept is based on the assumption that the time to market of a product increasingly determines its economic success. Its aim is to reduce the time of development from product to production line in only half the time. This objective can be achieved by introducing and applying a number of concepts, such as

- development of reusable standard modules,
- knowledge-based process design methodology,
- integration of experiment, modeling and design,
- modularization of the planning process,
- use of modular construction kits for laboratory equipment, planning elements, design and construction,
- increasing the degree of standardization and use of open standards,
- new concepts in automation technology, and
- numerical optimization instead of numerical simulation.

Just as old are the initial discussions on Industry 4.0 [3]. Industry 4.0 refers to the intelligent networking of machines and processes in industry using information and communication technology. There are many ways for companies to use intelligent networking. Among the possibilities are: flexible production, convertible factory, customer-centered solutions, optimized logistics, and use of data or resource-saving circular economy.

This is done by using a digital representation of all products and production processes. Strictly speaking, the properties and requirements of products are networked in the same way as the current settings and production recipes of the machines with their digital images. The machines, in turn, can use these digital images to select the optimum production process for the individual product and start it at the best time. This enables the optimization of operating processes and even creates completely new business models. There are many possibilities for companies to use such an intelligent networking. Especially outstanding for the process industry are: flexible production, convertible factories,

[1]Martin Bornemann-Pfeiffer, Dr. Simon Kern,
Dr. Michael Maiwald, Dr. Klas Meyer
michael.maiwald@bam.de
Bundesanstalt für Materialforschung und -prüfung (BAM), Richard-Willstaetter-Straße 11, 12489 Berlin, Germany.

[2]Martin Bornemann-Pfeiffer
Technical University of Berlin, Chemical and Process Engineering, Fraunhoferstraße 33–36, 10587 Berlin, Germany.

[3]Dr. Simon Kern
S-PACT GmbH, Burtscheider Straße 1, 52064 Aachen, Germany.

and predictive maintenance. Flexible production is most often translated with modular chemical production. For large-scale synthesis of bulk chemicals following established synthesis routes the conventional process development routes still work, but especially for high-margin specialty chemicals a high adaptability of processes and plants is desirable.

2 Advantages and Challenges of Modular Chemical Production

The factors for which a change to modular chemical production proves to be particularly favorable and economical [4–6] are outlined in Fig. 1. As mentioned at the beginning, the main motivating factors are high flexibility in a volatile market and a focus more towards individual customer-oriented products. A typical field are specialty chemicals with particularly high added value, e.g., up to concepts like personalized medicine in pharmaceutical production. Many demands from the 50 % idea can also be implemented very well in the modular approach, and they consistently bring together the steps of process and product development from R&D. With the separation of complex production plants into modules and devices, such approaches can also be applied advantageously in the brownfield sector. By increasingly making use of the enormous advantages of microreaction technology, such as the handling of very small quantities within a reactor, better heat dissipation or a much faster-acting process control, it is possible to realize safety-critical processes that would be inconceivable in a classical batch approach. Local flexibility and geographical mobility are another advantage of modular production. While technically feasible, current political situation of market-separating behavior of nations shows possible barriers in the realization of such concepts.

At the same time there are still some challenges that need to be overcome. One challenge, but as well an enormous opportunity, are open and standardized interfaces. While

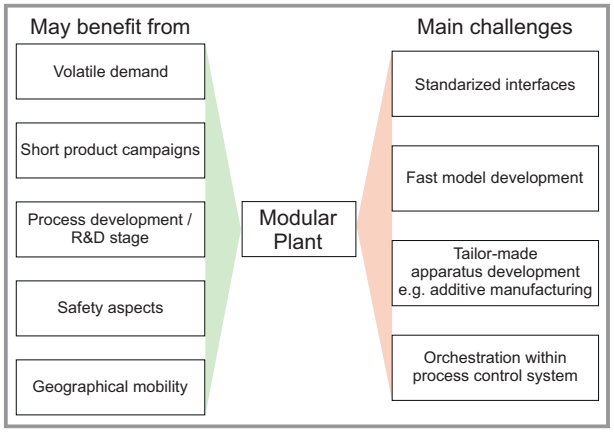


Figure 1. Advantages of modular chemical production and current challenges.

the established manufacturers of automation technology and equipment in particular have resisted this in order to preserve their proprietary world, it has been the small companies that have contributed to a fundamental rethink. In the meantime, the message has arrived that open and standardized interfaces are in everyone's interest and the piece of the cake is getting bigger for everyone – especially as the cake itself gets bigger.

Additive manufacturing [7, 8] is increasingly being used, because it offers advanced design freedom for customer- and product-specific reactors and analyzers for research and industry. In near future, such instruments can be considered as the heart of upcoming production facilities that perform automated chemical processes.

While the advantages of modular production are very attractive in terms of equipment technology, two crucial elements are still missing, which are briefly outlined in the following sections. At first, a flexible automation concept is required, because classical automation approaches are unsuitable for the modular concept due to lack of flexibility and high costs. On the other hand, monitoring specific information (i.e., "chemical" such as physico-chemical properties, chemical reactions, etc.) is a mandatory prerequisite to chemical process control especially if hazardous or short-lived intermediates are being formed. In contrast, most widespread sensors implemented today along with conventional plant instrumentation are still non-specific. [9]

2.1 Flexible Automation of Modular Plants

Modular chemical production along with modular automation reduces the complexity in engineering, setup and maintenance by internal functionality, as mentioned before. The classic hierarchical automation (automation pyramid), in which centralized control is exercised from a process control system right down to the field level of sensors and actuators with complex wiring and documentation, is no longer applicable in a modular concept. In 2013, a "Modular Automation" working group was established in the ZVEI [10] specialist area "Measurement Technology and Process Automation of the Automation Division" with the aim of cooperating closely with the NAMUR [11]. The working group published their concept for modular automation technology as white paper [12] that provides the required flexibility for modular plants. Much has happened since then, and considerable progress has been made from that time.

There are currently very promising, technical solutions in this context such as communication standards like OPC UA [13], module type package (MTP) [14], data exchange for the process industry (DEXPI), or concepts for fast generation and adaption of reliable models describing the process (digital twin) [15].

A uniform protocol and a uniform fieldbus are required for safe communication between all automation components.

Meanwhile the standard OPC Unified Architecture (OPC-UA) [16] is considered to be set and can be regarded as a small triumph of industry 4.0. Non-ethernet field buses are still dominant today against the background of a grown landscape in brownfield applications and the often very special requirements for power supply and explosion protection.

In the figurative sense, OPC-UA is comparable to the PDF standard, which defines the properties of graphical objects, e.g., print products. It is also independent of manufacturers or system suppliers, programming language, operating system or communication standard (e.g., fieldbus). The German Federal Office for Information Security (BSI) confirmed already in 2016 that OPC UA can be used to implement IT-safe industrial 4.0 communication. [17]

While OPC UA already allows data and workflows to be exchanged between automation components in a machine-readable format and these can be networked with each other, the so-called module type package (MTP) goes a considerable step further. Since 2014, Wago, an international supplier of automation technology, has been working on a concept for efficient individualization of process engineering systems together with TU Dresden and Helmut-Schmidt-Universität Hamburg. It is intended to enable manufacturers to combine autonomous modules into a flexible configured unit and, thus, significantly reduce the time-to-market of products. The decentralized intelligence for modular applications (DIMA) concept [18] uses the paradigm of service-oriented architecture (SOA) and builds on the standardization approach of NAMUR working group 1.12. The MTP is a digital description of the plant module and represents its functionality with all operational information for integration into the process control system. Therefore, it contains a vendor-neutral and functional description of the automation features. It can be generated by the engineering tool of the module. Through a simple import of the MTP into the process control engineering of the production plant the module can be easily integrated. For example, by using MTP the HMI (human-machine interface) of the module, which contains all static and dynamic information, can be generated automatically within the process control system. Furthermore, the MTP offers the possibility of a service-based control. The NAMUR specifies the MTP together with the ZVEI. [17]

Insufficient interoperability between computer-aided engineering (CAE) tools makes it difficult to plan, build and operate process plants across organizational boundaries, e.g., between different companies or even business units within the same company. For this reason, the DEXPI [19] working group within the ProcessNet community aims to develop a manufacturer-neutral exchange format for engineering data and documents and to implement it in interfaces of existing CAE tools. Currently, the focus is on the exchange of P&I diagrams including graphical layout and engineering data.

2.2 Interaction of the Observed Chemical Information with Process Models

The provocative abstract suggested very simplified that production modules are brought "to life (i.e., parameterizing them) with digitally accumulated process knowledge". This is precisely where we see the central challenge for modular automation: How can process knowledge and operational experience be brought into the lifeless modules? Furthermore, one of the visions of facilitated automation is hoping to accomplish decision support systems for processes and, in the end, even a troubleshooting if unforeseen deviations occur. One could become philosophical here, because the provision of module hardware will probably no longer be the key competence of the process industry in the future. It is exactly the orchestration and process knowledge that keeps the manufacturer close to the customer and protects him from becoming a contractor.

Instead, due to the high market requirements, nowadays preference is given to reliable operation, which is anchored in classical operational know-how. However, access to consistently compiled data alone is not enough to generate process understanding. The improvement of production parameters, space-time yield or energy efficiency can only be achieved by data- or knowledge-based models from the basic data via a more accurate description of the material on several scale levels.

To find an acceptable way to chemical process control and for sensors and actuators to better meet the requirements of digital transformation and the associated tasks in the future, they must be equipped with smart features. The benefits of smart field devices in the process industry and their communication options were first described in 2015 in the technology roadmap "Process Sensors 4.0" [20]. Recently, a position paper on sensor technology for the digitalization of chemical production plants was published [21].

For a holistic process analytical approach and such decision support systems, the semantic level (context information brought together with sensor data) must be considered beyond the pure interface definition (syntax, such as data acquisition, data connectivity, and data integrity). Data sources contain time-value pairs, but also discrete data from various data storage systems, which today are supplemented with increasingly complex, sometimes multidimensional data, for example from image-based techniques. Multivariate tools and algorithms are used for automated feature extraction, such as the extraction of chemical information from the above-mentioned data sources. Multivariate statistics such as PCA (principle component analysis), PLS (partial least squares) and LDA (latent discriminant analysis) form the initial basis for data analysis. Data preprocessing steps are mandatory and critical for these procedures. Modeling is currently done manually and is very complex and time-consuming.

The problem today is the non-optimal operation of processes, since external influences (fluctuating raw material

quality, *T*-influences by weather/energy supply) are not considered. Furthermore, no standardized interfaces between field device/data source, model and control system have been established yet. Specific data (i.e., chemical) are often not available or accessible due to lacking infrastructure.

Possible solutions can be found by using more specific data sources that become available through digital transformation. The temporary use of specific sensors, which may be dispensable again after data acquisition, will also be an important basis for the acquisition of context-related data and will support the generation of soft sensors.

In the context of machine learning (ML) and artificial intelligence (AI), there is currently some hope that data can be used meaningfully without classical modeling. However, the term "Big Data" as a prerequisite for data-driven evaluation procedures is not appropriate for the process industry, because even with quantitatively large data sets, information is typically only available for campaigns about a few batches with a series of measurement data that do not exhibit sufficient variance for a data-driven evaluation – not comparable with the data sets on the WWW or from large internet groups. [22, 23]

In the process technology environment, the term "Smart Data" is often used instead. Smart data includes, among other things, the clever selection of data for analysis and the combination of data-driven procedures and expert knowledge for their analysis. [24]

Even if the challenges of exchanging information and generating knowledge from it in the course of the digital transformation have been sufficiently solved, it should be pointed out that it will still be a further considerable challenge to use this knowledge on a cross-process and cross-plant basis. This step will once again be much more complex than the solution at process level.

2.3 Desire and Reality for Chemical Process Control

In order to achieve chemically specific measurements, sensors are needed that react directly or indirectly to changes in the target components – and this as specifically as possible (i.e., undisturbed by other components, the solvent or other disturbances) as well as with sufficient sensitivity. So-called direct analytical methods would be the optimum where the signal obtained is independent of matrix effects and is causally linked to an objective function – usually the concentration of a component in a multicomponent mixture. Furthermore, statements about the measurement uncertainty may be given. If a method causes indirect changes in the analytical signals, which are often described as nonlinear effects, then all correlations and interference effects would be completely known and could be represented in an analytical model for this component. Concentration-dependent changes of the refractive index or intermolecular interactions in optical spectroscopy are typical examples for such nonlinear effects, which end up in shifts or distortions of spectroscopic signals or nonlinear calibration curves for an observed target compound.

It should be clear that this consideration here can only be very general in order to illustrate the underlying principles. It is well known that real technical and complex reacting mixtures with all potentially occurring chemical and physical disturbances in the mixture and in the measurement process are deviating more or less strongly from the assumed conditions. In a controlled production, however, it is quite realistic that only minor deviations from the originally defined working region of the analytical method occur. This is referred to as "design space", which represents the variation of all critical process variables of that working region in the considered process step.

An excellent example of a direct analytical method is online nuclear magnetic resonance (NMR) spectroscopy. NMR spectroscopy is fulfilling most of the described relationships. Due to its direct correlation between the signal area in the spectrum and the number of nuclei in the active sample region, it allows for a calibration-free relative quantification compared to a "counting" of nuclear spins. In combination with a reference compound of known quantity or a single-point calibration, e.g., on a pure reactant, absolute quantification becomes feasible. This makes NMR spectroscopy a very promising method for online reaction monitoring applications. The application of NMR spectroscopy is currently in status TRL 7 (system prototype demonstration in operational environment). Work is presently underway to fully integrate an NMR analyzer and the associated data evaluation via MTP in the sense of a quality control and process control unit.

We have therefore taken the opportunity to very briefly represent the current state of the art of NMR instrumentation in Sect. 3 and present some practical examples in Sect. 4 to illustrate the principles and advantages of direct analytical methods.

3 Online NMR Spectroscopy as a Direct Process Analytical Method

3.1 NMR Instrumentation

NMR spectroscopy is a very versatile tool in the analytical toolbox and is widely used since many years especially in organic synthesis. The majority of performed sample analysis aim for qualitative information proving expected molecular structure and identity. However, the demand for quantitative NMR spectroscopy (qNMR) is rising.

Most NMR spectrometers operate on superconducting magnets to ensure high field strengths combined with a good field homogeneity. However, these instruments are large and can only be operated stationary in the lab, which impedes the use for online reaction monitoring directly in the field. Only a limited number of research groups specialized on that topic managed to develop a suitable

infrastructure around a high-field NMR spectrometer for monitoring reactions in the scale of laboratory to pilot plant. This situation has changed since the availability of compact benchtop NMR instruments based on rare-earth permanent magnets. These systems are easy to use and almost maintenance-free during operation. Currently, instrument manufacturers offer proton frequencies ranging from 43 MHz to 80 MHz announcing 100 MHz in very near future. Besides proton NMR capability most of the instruments allow for fixed or even variable options measuring popular X-nuclei like ^{13}C, ^{19}F, ^{31}P, and ^{29}Si.

3.2 Industrial Application of NMR-Spectroscopy

With these instruments, it is now possible to bring NMR spectroscopy directly into the field close to specialized laboratory equipment [25], pilot setups [26] and even industrial-scale manufacturing plants. Often integrated within a bypass flow configuration, instruments can be hyphenated by the use of specifically designed flow cells or regular polymer tubing based on process requirements. [27]

As the spectrometers offered on the market are usually intended to be used on a laboratory bench, additional protection equipment is required for a safe and reliable operation in a rough environment of an industrial site. A high level of automation and field communication ability needs to be established, as these systems need to operate on a 24/7 basis without having analytical NMR experts on-site. [28]

Besides protection of the instrument, most chemical production processes have very high safety demands, especially regarding explosion hazards. All electrical instrumentation, including analytical equipment, is required to comply with the latest guidelines according to ATEX or IECEx depending on the location and specified hazards on site. This needs to be proven before by certification at a notified body for these regulations. For the example of a fully automated, ATEX-compliant NMR analyzer module based on a laboratory device this was already successfully demonstrated within the EU project CONSENS – Integrated Control and Sensing. [29]

A major drawback of the current instruments on the market is the high sensitivity regarding temperature changes. To ensure field stability, permanent magnet systems need to be thermostated very precisely. Almost all benchtop instruments operate at a fixed magnet temperature slightly higher than room temperatures, some offering options to increase up to 60 °C. This is usually not a problem for regular operation with NMR tubes, but becomes highly relevant for reaction monitoring, as often dynamic situations arise from exo- or endothermic reaction steps, as well as process steps running at very different temperature ranges in fast sequences. Due to space limitations in the current design of magnets and probes, a sufficient insulation or even active temperature regulation between sample and magnet is almost impossible. Prototypes offering larger bore sizes could help to test suitable concepts tackling this issue and are highly desirable in the development of optimized setups for process monitoring.

4 Application Examples of Calibration-Free Chemical Process Control and Quality Control

4.1 Application 1: Combined Mixer Analyzer

Many continuous chemical reactions considered for flow chemistry follow fast kinetics. Hence, a consecutive placement of mixing and analysis device is required to gain insights into reaction mechanisms. Using NMR as analytical method, the flow cell is placed inside the magnet and, therefore, must fulfill additional requirements. A comprehensive overview about the design process and validation of a tailor-made flow cell (Fig. 2) made of ceramic material (Al_2O_3) is given in detail in a previous publication [29].

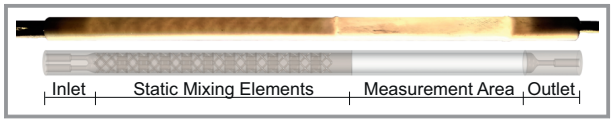


Figure 2. Photograph and CFD model of an additively manufactured flow cell consisting of a mixing and a measurement area. Sufficient mixing is ensured through consecutive SMX-type mixing elements. The application of a sapphire glass cylinder in the measurement area leads to high quality spectra.

ATEX-compliant integration of the assembly is ensured by firmly bonded, patented connection [30] to stainless steel tubes. The custom-made design of a flow reactor especially suited for the need of the employed analytical method provides great advantages over off-the-shelf devices, e.g., improved closeness to the actual chemical reaction [31]. Furthermore, the devices can be quickly adapted towards changing process conditions or improvements being implemented in a fast manner by simply reprinting the desired apparatus.

4.2 Application 2: Model-Based Approaches for Spectra Evaluation

Signals observed on compact NMR spectrometers tend to spread and overlap due to the low magnetic field of permanent magnets compared to high-field NMR devices. The large amounts of data generated in process analytical applications lead to complex data sets with numerous overlaps in the spectrum. This type of data is usually subject to many effects in the NMR spectrum caused by inhomogeneities in the magnetic field, e.g., from temperature fluctuations of the magnet or solid particles contained in the sample. These nonlinear effects result in peak shape distortions (peak

-widening or asymmetric peaks) or peak shifts, which must be considered by a robust data evaluation method.

Model-based approaches are getting wider acceptance as a robust alternative to the established peak integration. Quantum mechanical principles are invariant with respect to the magnetic field strength. They take advantage from the quantum mechanical properties of the spectra and offer identification of individual components based on spectral parameters. [32]

Using a Bayesian approach, a general model for an NMR signal was published that considers the effects of chemical shifts, relaxation, line shape imperfections, phasing, and baseline distortions [33, 34]. Indirect hard modeling (IHM) enables the analysis of complex spectra acquired on low-field instruments (Fig. 3) and was successfully demonstrated in both academic [35, 36] and industrial applications [37, 38]. IHM is based on the idea that the spectrum is composed of components modeled with a collection of peak-shaped signals, i.e., Pseudo-Voigt functions with certain positions, width, heights, and Gaussian-Lorentzian ratios (Fig. 3a and b). By adjusting the peak parameters (Fig. 3c), the model is fitted to the experimental data (Fig. 3e), which finally provides concentrations of the components in the analyzed sample (Fig. 3d). Within such a hard model, the shape of each component is preserved by fixing peak area ratios of individual peaks. [39]

Multiplets or even higher-order spectra can be described by combinations of these peak functions. This offers a fully automated approach to resolve overlapping component signals, which are subject to the abovementioned nonlinear effects. In a recent study of a lithiation reaction step, the IHM approach could easily adopted to various starting materials and achieved root-mean-square errors (RMSE) for the concentration measurements of each reaction system in the lower mmol L^{-1} range. [29]

4.3 Application 3: Online Reference Data for Method Transfer

In order to achieve chemical process control, the process does not necessarily have to be permanently observed with direct analytical methods, as these are still relatively unestablished and expensive today. One conceivable variant is to use calibration-free methods only in an initial learning phase and to transfer the derived data to operationally proven analyzers (or even soft sensors) – provided that these are capable of detecting specific changes in the design space either directly or indirectly.

In recent years, optical spectroscopic methods such as near-infrared (NIR), Raman and mid-infrared spectroscopy (MIR or IR) have been increasingly used for online monitoring of product quality in industry [40] and users have gained experience. For complex mixtures, the calibration of optical spectroscopic analyzers in general is based on a multivariate approach. In order to cover all possible chemical states of the reaction mixture in a calibration model, a design of experiments is typically used. Often, the actual plant setup needs to be operated in unfavorable states to ensure covering the full design space in the development of these calibration models, which is an important economic factor. For each variation in the chemical structure of the raw materials, analytical data (spectra) in combination with reference data are required to develop and maintain the calibration models. With the analytical instrumentation getting more and more affordable, the high amount of work establishing calibration models gets less reasonable, especially when thinking about flexible production setups with a high number of different measurement positions. Today, reference values for calibration are usually obtained from labor-intensive laboratory experiments and offline analysis (e.g., HPLC or GC-MS), which requires sampling from the continuous production stream. Since combined sampling errors are usually one or two orders of magnitude larger than the analytical uncertainty, the sampling procedure has the dominant influence on data quality [41].

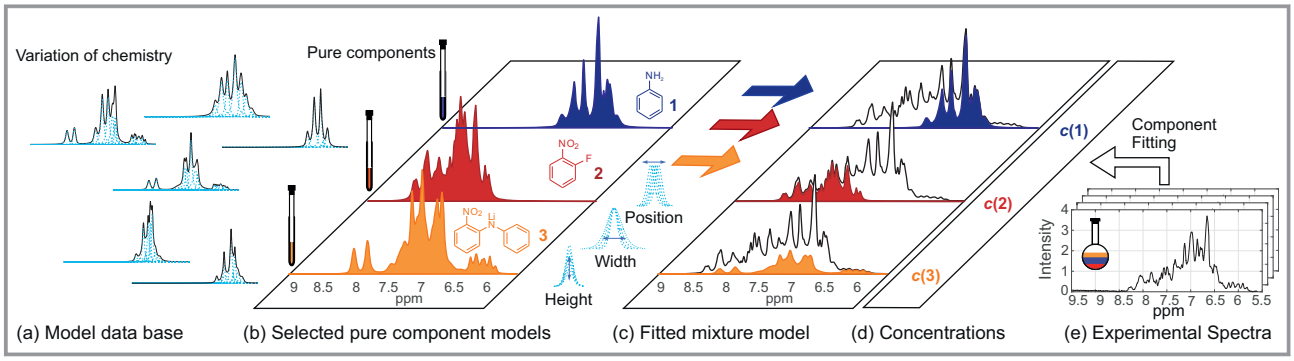


Figure 3. Indirect hard modeling (IHM) workflow for quantitative evaluation of NMR spectra (e) in order to obtain species concentrations (d) by building a mixture model (c). Relevant pure component models (b) for each process can be selected from pure a component model database (a) and employed together with model constraints. Cyan dashed lines represent peak functions of each spectral model.

To overcome this, direct analytical methods like NMR spectroscopy can be used to gather reference data on the running process for the development of multivariate models. This was demonstrated in the calibration of a NIR analyzer implemented along with a benchtop NMR device on a modular plant setup. It could be shown that the consideration of sensitive intermediate species accessible in the NMR spectrum could improve the quality of the multivariate model compared to reference data obtained from HPLC after quenching the process sample. [29]

4.4 Application 4: Machine-Assisted Model Building

Artificial neural networks (ANNs) have the potential to extract valuable process information. ANN approaches can be advantageous compared to model-based approaches since they require very little computing power for predictions and are orders of magnitudes faster than, e.g., IHM. This is advantageous if the prediction is to be implemented, e.g., in an embedded system with limited performance. Another advantage is that ANNs do not rely on discrete decisions of a nonlinear optimization scheme, which is used during the spectral model fitting within model-based approaches. These nonlinear optimization schemes can face challenges, e.g., fitting impurities beneath large signals.

To predict the quantitative information from complex NMR spectra large training datasets are required for such data driven methods. The application of ANNs for the quantitative evaluation of spectroscopic data has already been demonstrated on the past [42–44]. Our recent work shows a novel training concept for NMR spectroscopy using machine learning, which needs less training data than usual approaches [45]. To overcome the issue of the large amount of training data simulated variants of the measured data (i.e., synthetic NMR spectra) were calculated. This data augmentation procedure for the generation of synthetic but physically based NMR is based on using spectral hard models as described in the section above for forward prediction. By this the initial training dataset can be sized and distributed along various prediction variables arbitrarily (see Fig. 4). This recent study shows that the application of ANN approaches to low-field NMR data with limited experimental data is in general possible. However, a limitation of the ANN methodology is that the resulting model may only reproduce those changes that are within the training label space and, thus, the application to ranges outside the training dataset will be limited.

5 Conclusions

An increasing flexibility of modular chemical production comes along with the demand for flexible online process analytical instrumentation. Direct analytical methods like NMR spectroscopy can help to improve process knowledge and maintain product quality without the need for extensive calibration effort. Even when not implemented permanently, direct analytical methods can be used for acquiring reference data for the development of model-based approaches for other PAT methods (like optical spectroscopy) or even combination of conventional process sensors (soft-sensing). Currently, connectivity within the plant setups is often limited, which impedes the fusion of data from the large number of already available sensors. In the future, data availability within the plant setup will be not a problem anymore, allowing new concepts of process monitoring and control feedback. Process knowledge from the initial development as well as gained knowledge over the time of operation will be available in a digital representation of the setup and continuously improved. The ultimate goal is the full integration and intelligent networking of systems and processes. [46]

The process industry is facing changes that will take place over a long period of time. These require a strong research and design effort. Digitalization cannot be achieved on its own, it can only be shaped together with all parties engaged.

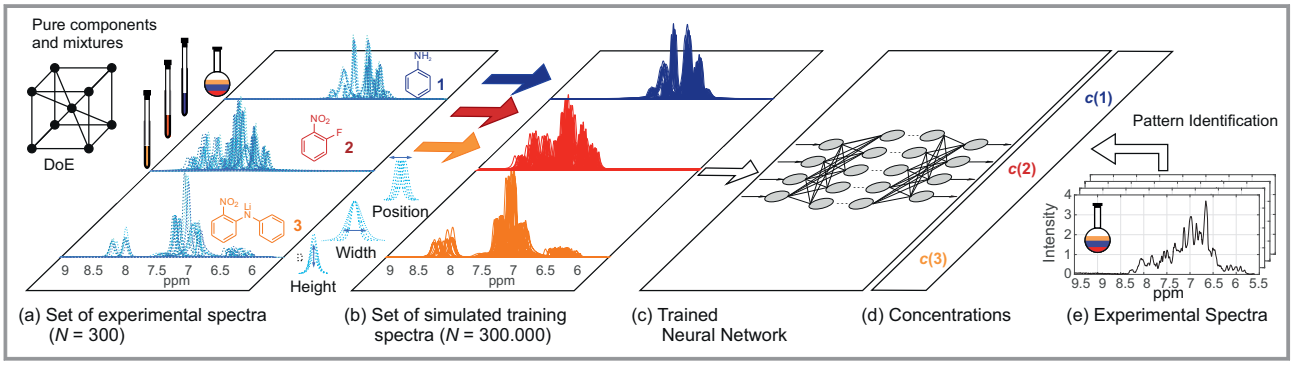


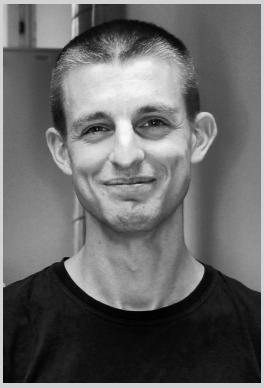
Figure 4. Artificial neural network (ANN) workflow for quantitative evaluation of experimental NMR spectra (e) in order to obtain species concentrations (d) by identifying pure components in a mixture (c). Through variation of peak function parameters generated synthetic training spectra (b) based on a limited model data base (a) used for setup and training of a neural network. Cyan dashed lines represent peak functions of each spectral model.

We thank Björn Hagedorn and Lukas Wander for their experimental work and Prof. Dr.-Ing. Matthias Kraume for many discussions and the support of collaborative theses, which so far have led to three joint publications. [20, 47, 48]. Open access funding enabled and organized by Projekt DEAL.

After working two years for a gas network operator, **Martin Bornemann-Pfeiffer** studied chemical & process engineering at Technical University Berlin and received a master's degree in 2018. He joined BAM in 2017 and is currently working as a PhD student in cooperation with Technical University Berlin. His research focuses include process automation with low-field NMR spectroscopy and digital representation of processes.

Simon Kern received a master degree in bioprocess engineering at Technische Universität Hamburg-Harburg. He worked 2015–2019 as PhD student with BAM and Technische Universität Berlin focusing on process control with low-field NMR spectroscopy. Since 2019 he is working as an application scientist at S-PACT GmbH.

After research positions at the University of Stuttgart and Merck KGaA, **Michael Maiwald** is since 2008 Head of Division Process Analytical Technology at Bundesanstalt für Materialforschung und -prüfung (BAM). His research interests are online NMR and optical spectroscopy, process analytical technology, chemometrics, and process automation.



Klas Meyer received his diploma in chemistry and his PhD from Humboldt University Berlin and he joined BAM from 2012–2017 focusing on high-pressure NMR spectroscopy for gas analysis and for process industry. He joined Magritek GmbH in Aachen as application scientist and came back to BAM in 2018 for quantitative and online NMR spectroscopy and automation.

References

[1] K. Mädefessel-Herrmann, *Die 50-Prozent-Idee: Vom Produkt zur Produktionsanlage in der Hälfte der Zeit*, Chemanager, June 28, **2012**. www.chemanager-online.com/themen/produktion/die-50-prozent-idee-vom-produkt-zur-produktionsanlage-der-haelfte-der-zeit (accessed July 12, 2020)
[2] *Die 50-%-Idee – Vom Produkt zur Produktionsanlage in der halben Zeit*, ProcessNet, November 14, **2009**. https://processnet.org/processnet_media/Veranstaltungen/48Tutzing/die+50prozent_idee-p-1159.pdf (accessed July 12, 2020)
[3] *Platform Industrie 4.0*, Federal Ministry for Economic Affairs and Energy, Berlin. www.plattform-i40.de/PI40/Navigation/EN/Home/home.html (accessed July 12, 2020)
[4] M. Baldea, T. F. Edgar, B. L. Stanley, A. A. Kiss, Modular Manufacturing Processes: Status, Challenges, and Opportunities, *AIChE J.* **2017**, *63*, 4262–4272.
[5] T. Becker, S. Lier, B. Werners, Value of modular production concepts in future chemical industry production networks, *Eur. J. Oper. Res.* **2019**, *276*, 957–970.
[6] *Flexible chemical production by modularization and standardization – status quo and future trends*, DECHEMA e.V., Frankfurt a. Main **2016**. https://dechema.de/dechema_media/modularplants.pdf (accessed July 12, 2020)
[7] C. Parra-Cabrera, C. Achille, S. Kuhn, R. Ameloot, 3D printing in chemical engineering and catalytic technology: structured catalysts, mixers and reactors, *Chem. Soc. Rev.* **2018**, *47*, 209–230.
[8] S. Rossi, A. Puglisi, M. Benaglia, Additive Manufacturing Technologies: 3D Printing in Organic Synthesis, *ChemCatChem* **2018**, *10*, 1512–1525.
[9] M. Maiwald, P. Gräßer, L. Wander, N. Zientek, S. Guhl, K. Meyer, S. Kern, Strangers in the Night – Smart Process Sensors in Our Current Automation Landscape, *Proceedings* **2017**, *1*, 628. DOI: https://doi.org/10.3390/proceedings1040628
[10] www.zvei.org (accessed July 12, 2020)
[11] www.namur.net/en/index.html (accessed July 12, 2020)
[12] *Module-Based Production in the Process Industry – Effects on Automation in the "Industrie 4.0" Environment*, White Paper, ZVEI – Zentralverband Elektrotechnik- und Elektronikindustrie e.V., Frankfurt a. Main **2015**. www.zvei.org/en/press-media/publications/white-paper-module-based-production-in-the-process-industry-effects-on-automation-in-the-industrie-40-environment (accessed July 12, 2020)

[13] www.opcfoundation.org (accessed October 17, 2020)
[14] www.namur.net/en/focus-topics/automation-modular-plants.html (accessed July 12, 2020)
[15] G. Santillán Martínez, S. Sierla, T. Karhela, V. Vyatkin, Automatic Generation of a Simulation-Based Digital Twin of an Industrial Process Plant, in *IECON 2018–44th Annual Conference of the IEEE Industrial Electronics Society*, IEEE, Piscataway, NJ **2018**. DOI: https://doi.org/10.1109/IECON.2018.8591464
[16] S. Wassilew, L. Urbas, J. Ladiges, A. Fay, T. Holm, Transformation of the NAMUR MTP to OPC UA to allow Plug and Produce for Modular Process Automation, in *2016 IEEE 21st International Conference on Emerging Technologies and Factory Automation (ETFA)*, IEEE, Piscataway, NJ **2016**. DOI: https://doi.org/10.1109/ETFA.2016.7733749
[17] *Security analysis OPC UA*, Federal Office for Information Security (BSI), Bonn **2015**. www.bsi.bund.de/DE/Publikationen/Studien/OPCUA/OPCUA_node.html (accessed October 17, 2020)
[18] www.wago.com/global/digitization/convertibility (accessed October 17, 2020)
[19] https://dexpi.net/ (accessed October 17, 2020)
[20] *Technologie-Roadmap Prozess-Sensoren 4.0*, VDI/VDE-Gesellschaft Mess- und Automatisierungstechnik und NAMUR – Interessengemeinschaft Automatisierungstechnik der Prozessindustrie, Düsseldorf **2015**.
[21] U. Hampel et al., *Sensorik für die Digitalisierung chemischer Produktionsanlagen*, Positionspapier, DECHEMA e.V., Frankfurt a. Main **2020**.
[22] J. Folmer, I. Kirchen, E. Trunzer, B. Vogel-Heuser, T. Pötter, M. Graube, S. Heinze, L. Urbas, M. Atzmüller, D. Arnu, Big und Smart Data, *atp Mag.* **2017**, *59 (1–2)*, 58–69. DOI: https://doi.org/10.17560/atp.v59i01-02.623
[23] E. Trunzer, I. Weiß, T. Pötter, C. Vermum, M. Odenweller, S. Unland, D. Schütz, B. Vogel-Heuser, Big Data trifft Produktion, *atp Mag.* **2019**, *61 (1–2)*, 90–98. DOI: https://doi.org/10.17560/atp.v61i1-2.2394
[24] T. Eifert, K. Eisen, M. Maiwald, C. Herwig, Current and Future Requirements to Industrial Analytical Infrastructure – Part 2: Smart Sensors, *Anal. Bioanal. Chem.* **2020**, *412*, 2027–2035.
[25] P. Sagmeister, J. D. Williams, C. A. Hone, C. O. Kappe, Laboratory of the future: a modular flow platform with multiple integrated PAT tools for multistep reactions, *React. Chem. Eng.* **2019**, *4*, 1571–1578.
[26] W. G. Lee, M. T. Zell, T. Ouchi, M. J. Milton, NMR spectroscopy goes mobile: Using NMR as process analytical technology at the fume hood, *Magn. Reson. Chem.* **2020**, *58 (12)*, 1193–1202. DOI: https://doi.org/10.1002/mrc.5035
[27] F. Dalitz, M. Cudaj, M. Maiwald, G. Guthausen, *Prog. Nucl. Magn. Reson. Spectrosc.* **2012**, *60*, 52–70. DOI: https://doi.org/10.1016/j.pnmrs.2011.11.003
[28] K. Meyer, S. Kern, N. Zientek, G. Guthausen, M. Maiwald, Process control with compact NMR, *Trends Anal. Chem.* **2016**, *83*, 39–52.
[29] M. Bornemann, S. Kern, N. Jurtz, T. Thiede, M. Kraume, M. Maiwald, Design and Validation of an Additively Manufactured Flow Cell–Static Mixer Combination for Inline NMR Spectroscopy, *Ind. Eng. Chem. Res.* **2019**, *58*, 19562–19570.
[30] M. Bornemann et al., Druckstabile 3D gedruckte NMR-Durchflusszelle, *European Patent EP3679384A1*, **2020**.– https://worldwide.espacenet.com/patent/search/family/063586673/publication/EP3679384A1?q=3679384
[31] M. C. Maier, R. Lebl, P. Sulzer, J. Lechner, T. Mayr, M. Zadravec, E. Slama, S. Pfanner, C. Schmölzer, P. Pöchlauer, C. O. Kappe, H. Gruber-Woelfler, Development of customized 3D printed stainless steel reactors with inline oxygen sensors for aerobic oxidation of Grignard reagents in continuous flow, *React. Chem. Eng.* **2019**, *4*, 393–401.
[32] M. Tiainen, P. Soininen, R. Laatikainen, Quantitative quantum mechanical spectral analysis (qQMSA) of 1H NMR spectra of complex mixtures and biofluids, *J. Magn. Reson.* **2014**, *242*, 67–78.
[33] Y. Matviychuk, E. von Harbou, D. J. Holland, An experimental validation of a Bayesian model for quantification in NMR spectroscopy, *J. Magn. Reson.* **2017**, *285*, 86–100.
[34] Y. Matviychuk, E. Steimers, E. von Harbou, D. J. Holland, Improving the accuracy of model-based quantitative nuclear magnetic resonance, *Magn. Reson.* **2020**, *1 (2)*, 141–153.
[35] A. Friebel, E. von Harbou, K. Münnemann, H. Hasse, Online process monitoring of a batch distillation by medium field NMR spectroscopy, *Chem. Eng. Sci.* **2020**, *219*, 115561.
[36] A. Michalik-Onichimowska et al., "Click" analytics for "click" chemistry – A simple method for calibration-free evaluation of online NMR spectra, *J. Magn. Reson.* **2017**, *277*, 154–161.
[37] S. Kern, K. Meyer, S. Guhl, P. Gräßer, A. Paul, R. King, M. Maiwald, Online low-field NMR spectroscopy for process control of an industrial lithiation reaction – automated data analysis, *Anal. Bioanal. Chem.* **2018**, *410 (14)*, 3349–3360.
[38] S. Kern, L. Wander, K. Meyer, S. Guhl, A. R. Gottu Mukkula, M. Holtkamp, M. Salge, C. Fleischer, N. Weber, R. King, S. Engell, A. Paul, M. Pereira Remelhe, M. Maiwald, Flexible automation with compact NMR spectroscopy for continuous production of pharmaceuticals, *Anal. Bioanal. Chem.* **2019**, *411 (14)*, 3037–3046.
[39] E. Kriesten, F. Alsmeyer, A. Bardow, W. Marquardt, Fully automated indirect hard modeling of mixture spectra, *Chemom. Intell. Lab. Syst.* **2008**, *91 (2)*, 181–193.
[40] L. L. Simon et al., Assessment of Recent Process Analytical Technology (PAT) Trends: A Multiauthor Review, *Org. Process Res. Dev.* **2015**, *19 (1)*, 3–62.
[41] K. H. Esbensen, P. Paasch-Mortensen, Process Sampling: Theory of Sampling – the Missing Link in Process Analytical Technologies (PAT), in *Process Analytical Technology* (Ed: K. A. Bakeev), Wiley, Oxford **2010**, 37–80.
[42] E. C. Ferreira, D. M. B. P. Milori, E. J. Ferreira, R. M. Da Silva, L. Martin-Neto, Artificial neural network for Cu quantitative determination in soilusing a portable laser induced breakdown spectroscopy system, *Spectrochim. Acta, B* **2008**, *63*, 1216–1220.
[43] T. Väänänen, H. Koskela, Y. Hiltunen, M. Ala-Korpela, Applicationof quantitative artificial neural network analysis to 2D NMR spectraof hydrocarbon mixtures, *J. Chem. Inf Comput. Sci.* **2002**, *42*, 1343–1346.
[44] J. R. Long, V. G. Gregoriou, P. J. Gemperline, Spectroscopic calibrationand quantitation using artificial neural networks, *Anal Chem.* **1990**, *62*, 1791–1797.
[45] S. Kern, S. Liehr, L. Wander, M. Bornemann-Pfeiffer, S. Müller, M. Maiwald, S. Kowarik, Artificial neural networks for quantitative online NMR spectroscopy, *Anal. Bioanal. Chem.* **2020**, *412*, 4447–4459.
[46] M. Maiwald, Voll integrierte und vernetzte Systeme und Prozesse – Perspektive: Smarte Sensorik, Aktorik und Kommunikation, *atp Mag.* **2018**, *60 (10)*, 70–85.
[47] N. Zientek, C. Laurain, K. Meyer, M. Kraume, G. Guthausen, M. Maiwald, Simultaneous ^{19}F-^{1}H Medium Resolution NMR Spectroscopy for Online Reaction Monitoring, *J. Magn. Reson.* **2014**, *249*, 53–62.
[48] N. Zientek, C. Laurain, K. Meyer, A. Paul, D. Engel, G. Guthausen, M. Kraume, M. Maiwald, Automated data evaluation and modelling of simultaneous ^{19}F–^{1}H medium-resolution NMR spectra for online reaction monitoring, *Magn. Reson. Chem.* **2015**, *54*, 513–520.

