

# Process control with compact NMR

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## Abstract

Compact nuclear magnetic resonance (NMR) instruments make NMR spectroscopy and relaxometry accessible in industrial and harsh environments for reaction and process control. An increasing number of applications are reported. To build an interdisciplinary bridge between "process control" and "compact NMR", we give a short overview on current developments in the field of process engineering such as modern process design, integrated processes, intensified processes along with requirements to process control, model based control, or soft sensing. Finally, robust field integration of NMR systems into processes environments, facing explosion protection or integration into process control systems, are briefly discussed.

## Highlights

- Compact NMR is extremely useful for the process industry
- This review builds an interdisciplinary bridge between process control and compact NMR
- Read about contemporary automation and process control

## Keywords

Process control, compact NMR, process analytical technology, low-field NMR spectroscopy, low-field NMR relaxometry, flow-NMR, data analysis, chemometrics, advanced process control, Industrie 4.0

## 1 Introduction

The future competitiveness of the process industry, i.e., the industrial branches of chemical, pharmaceutical, petro-chemical production, gas processing, food, pulp, paper, glass, steel, and cement production as well as 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 and are of particular interest to 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.

Quantitative online nuclear magnetic resonance (NMR) spectroscopy is a powerful tool for the investigation of fluid process streams 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 – provided that 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. Additionally, NMR spectroscopy provides orthogonal, but complimentary physical information to conventional, e.g., optical spectroscopy. It increases the accessible information for technical processes, where aromatic-to-aliphatic conversions or isomerizations occur and conventional methods fail due to only minor changes in functional groups. Compared to the most sensitive online analytical methods, such as laser spectroscopy for gases or chromatography, NMR exhibits a comparatively poor sensitivity with current minimum limits of detection somewhere in the 10-50 ppm (mol/mol) region for high field instruments and 0.2-0.5 % (mol/mol) for low field instruments.

Time domain NMR is another way of using NMR in quality and process control. Most low-field NMR instruments currently observe  $^1\text{H}$  and  $^{19}\text{F}$  NMR combined with relaxation or diffusion weighing of the acquired signals. Mainly three different NMR approaches remain to provide so far as contrast parameters. The first is the signal amplitude, which is proportional to the number of spins in the measured or sensitive volume of the probe. Most often the samples under investigation do not

contain just one species with  $^1\text{H}$  so that a contrast parameter is needed for discrimination of different  $^1\text{H}$  signals. Relaxation properties, especially transverse relaxation  $T_2$  are suitable for such a contrast creation, mainly for highly viscous fluids and solids. However, the approach of measuring at least two independent NMR parameters has been shown to be successful in several cases such as, e.g., utilizing diffusion and relaxation differences.

Hitherto, automated data preparation and analysis are cornerstones for a breakthrough of NMR techniques for process control. Luckily this has been recognised by the user and research community, instrument manufacturers, and NMR software vendors. Particularly, robust chemometrics as well as automated signal processing methods have to be (further) developed especially for NMR spectroscopy in process control. Traditional approaches do not cope well with temperature, pressure, or concentration induced drifts of NMR spectra along the axis as well as individual shifting NMR signals of individual analytes. In section 3.4 and 4.1 we briefly outline the currently available techniques.

0.1 % sensitivity (i.e., precision) on a molar basis is a typical target specification for concentration uncertainties in industrial reaction monitoring. NMR here competes against chromatographic methods, which are conventionally used for process control in order to find the optimal cut-off point for any reaction, where all educts have quantitatively reacted and at the same time no by-products arise. This is an enormous challenge for further instrument and data analysis development.

## 2 Process Control

Since currently there is a considerable trend to use compact NMR spectroscopy for reaction monitoring and process control, this section gives a short overview on current developments in the field of process engineering, such as modern process design, integrated processes (e.g., reactive separation processes), and intensified processes (cf., 2.2) along with requirements to process control, model based control, and soft sensing (cf., 2.2.3). Finally, in section 2.4 current and future requirements to sensors are briefly introduced, like discussed for the future projects "Industrie 4.0" facilitating the vision and execution of a "Smart Factory" as well as "Industrial Internet of Things" (IIoT). Industrie 4.0 is the fourth industrial revolution. It had been defined as a collective term for technologies and concepts of value chain organization which draws together Cyber-Physical Systems, the Internet of Services, and the Internet of Things. The latter – called Industrial Internet of Things (IIoT) when applied to manufacturing or process industry – is based on intelligent field devices, digital field networks, Internet Protocol (IP)-enabled connectivity, and web services.

## 2.1 Contemporary Process Engineering

Process engineering focuses on the design, operation, control, and optimization of chemical, physical, or biological processes. The discipline involves creating production facilities that translate raw materials into value-added products along the supply chain. Such conversions typically take place in repeated reaction and separation steps – either in batch or continuous processes. The end products of a chemical production facility are the result of several production steps that are connected not only in a sequential fashion, but also involve recycling of unused raw materials and by-products, as well as waste treatment stages. Production processes in process industry are particularly disturbed by variations in feed-stocks and other influences that impact the product quality. An integrated process control approach enables constant product quality and prevents out-of-spec production by effectively compensating for such process variations. In a conventional approach quality is determined by withdrawing samples from material streams and conducting offline analytics, which is called in-process control or at-line or off-line control. By applying "Quality by Design" (QbD) approaches quality can significantly improve to generate less waste, reduce reprocessing of substandard material, and create products of superior quality.

Nowadays, optimized process design relies heavily on computer aided tools, which account for, e.g., mass transfer, thermodynamic, kinetic, and other physical properties of the treated materials. Typically, a sufficient understanding of such properties is available and implemented in dynamic numeric models. (However, a good number of classical processes are not completely understood in such manner.) Dynamic models are in turn the essential basis for optimized process and plant design. Unfortunately, they are only sparsely used for process control. A definition from Lee [1] brings this to a contemporary level:

"Cyber-Physical Systems (CPS) 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".

## 2.2 Integrated Process Design and Intensified Processes

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.

### 2.2.1 Intensified Continuous Processes

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, leads to better product uniformity, and drastically reduces the consumption of raw materials and energy. Flexible (modular) chemical plants can produce different products using the same equipment with short down-times between campaigns, and quick introduction new products to the market. Typically, such plants have smaller scale than big size plants for basic chemicals but still are capable to produce kilograms to tons of specialty products each day. Such flexible (modular) plants can be provided in containers of the size of freight containers.

However, 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.

### 2.2.2 Integrated Processes

Another achievement of contemporary process engineering is the shift towards integrated processes combining reaction and separation in one single unit. This trend is motivated by a couple of benefits at the same time, such as a reduction in equipment and plant size as well as improvement of process efficiency and hence, better process economy. Reactive distillation is a eminent example of a reactive separation process. Especially for equilibrium reactions like esterifications, ester hydrolyses, or etherifications, the combination of reaction and separation within a dedicated zone of a reactive distillation column is a well-known alternative to conventional processes with sequential reaction and separation steps [2]. Typically, non-ideal aqueous–organic mixtures are formed which tend to form azeotropes, which can be overcome using membrane separations (e.g., pervaporations or vapor permeations) [3]. On the other hand, undesired effects may also occur, such as an increasing byproduct formation. Consequently, a hybrid process consisting of membrane-assisted reactive distillation contributes to sustainable process improvement due to arising synergy effects and allows reduction of investment and operational costs. A review of hybrid processes combining pervaporation with one or more other separation technologies can be found in Lipnizki, Field and Ten [4]. In recent years, a considerable number of papers have been published that contain well-documented information on reactive distillation experiments in laboratory scale, accompanied by simulation results, which are usually in good agreement with the experimental data. Modeling and simulation of the reactive distillation process, carried out both with the equilibrium stage and with the rate-based approach, are based on careful experimental and modeling work on the underlying vapor-liquid and liquid-liquid equilibria and the reaction equilibrium and kinetics. It is shown that the

separation side of the process can be well described with conventional methods. In contrary, a proper description of reaction kinetics under such conditions is complicated since laboratory experiments show very different results compared to that derived from real process conditions. Understanding the reaction is the key to successful design and scale-up of heterogeneously catalyzed reactive distillation.

### 2.2.3 Towards Continuous Pharmaceutical Manufacturing

According to ICH Q8 (R2), "quality" is the suitability of either a drug substance or drug product for its intended use (ICH: International Conference on Harmonization). This term includes attributes, such as identity, strength, and purity [5]. Before the launch of the PAT (process analytical technology) Initiative [6], pharmaceutical production was confronted with challenges like drug shortages due to manufacturing difficulties, process deviations coupled with frequent inconclusive investigations, batch failures and rejections, in-process test debates (e.g., blend uniformity), slow and protracted cGMP (current good manufacturing practice) remediation, warning letters, and others.

The science-based regulatory guidances such as the FDA (US Federal Drug Administration) and ICH "Process Analytical Technology (PAT) guidance" [6] have recognized spectroscopic techniques as potentially useful tools on building quality into the product and manufacturing processes, as well as continuous process improvements. The goal of PAT is to enhance understanding and thereby control the manufacturing process. The basic – and frequently cited – approach comprises:

"The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It is important to note that the term analytical in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. The goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design." [6]

The PAT initiative is discussed insistently and led to increased research activities and to a new awareness of all participants in the regulated field. The intense engagement with this subject continues to date. Important precursors are:

- European Medicines Agency (EMA), European Union [7]
- Pharmaceutical and Medical Devices Agency (PMDA), Japan [8]
- International Society of Pharmaceutical Engineering (ISPE), U.S.A. [9]

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), supported by FDA, EMA, and PMDA [10]

The common future vision in pharmaceutical production 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 (featuring less operator intervention and less down time), and end to end process understanding over product lifecycle, future knowledge, and faster product to market. It is assumed to reduce the quality control costs from 20–30 % today to fewer than 5 % within a CM concept.



**Figure 1:** "Evolution" starting from a conventional approach, mainly based on "Quality by Testing" (left), presently targeted approach using the toolboxes Quality by Design and Process analytical Technology (middle), leading to the future Vision Continuous Manufacturing (right).

#### 2.2.4 Flow Chemistry

Core activities of process chemistry involve the synthesis of drug candidates at a scale that supports clinical evaluations and the creation of a manufacturing process that is safe, robust, and cost effective. The acquisition and creation of platform chemical technologies that enable rapid problem solving through the use of high-throughput experimentation will continue to be an important focus going forward. Linking and deploying platforms throughout the discovery-development continuum is expected to enable drug discovery. This has successfully been shown by developing both chemistries and technologies to achieve novel and more efficient routes towards specific targets. In recent years,

flow chemistry has emerged as a useful tool. [11-14] Virtually all active pharmaceutical ingredients (APIs) are still produced by using multiple distinct batch processes. To date, methods for the divergent multistep continuous production of customizable small molecules are not available.

Serving as an example, a chemical assembly system was developed by Ghislieri et al., in which flow-reaction modules were linked together in an interchangeable fashion to give access to a wide breadth of chemical space. Control at three different levels – choice of starting material, reagent, or order of reaction modules – enabled the synthesis of five APIs that represent three different structural classes. [15]

### **2.3 Contemporary Automation and Process Control**

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.

Classical control schemes based on standard instrumentation (e.g., measurements of temperatures, pressures, or flow rates) have to be carefully engineered in order to avoid violations of the constraints which cannot be monitored continuously due to the lack of suitable sensors. The set-points of control loops must be chosen such that the process is kept at a safe distance from the constraints without having precise information about the closeness to these constraints. To develop and implement such control structures requires experience, case-by-case engineering, and trial and error under real process conditions until a working, but still sub-optimal solution is obtained.

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 has to be merged. In addition, their adaptation causes a high effort during the life cycle of the process. This calls 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 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 (PID controllers (proportional–integral–derivative controller), cascade and override structures) 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.

Advanced control strategies have to be built upon empirical – often data-based – models which describe cause-effect mappings between the degrees of freedom of the process and the product properties in a black-box fashion. Chemometric techniques for the derivation of empirical models (e.g., PLS (Partial Least Squares), PCA (Principal Component Analysis), cf., 3.4.2) 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. The development of such models requires significant experimental work, and the 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 that make use of the novel sensors, like online NMR.

Chemical engineering problems, which aim at an accurate description of process performance based on rigorous thermodynamics, reaction kinetics, or mass and heat transfer modeling, result in highly nonlinear and nonconvex large-scale problems. The computational effort for the solution of these problems increases exponentially with the number of discrete variables, and deterministic optimization methods are mostly limited to local optimization. When advanced sensing technology is available, the individual units can be controlled such that the outgoing streams satisfy tight specifications. For example global mass and energy balances, local response surfaces that relate specifications of outgoing and ingoing streams to the consumption of energy and the cost of production, or simple dynamic models of the behavior of the process stream (i.e., delays, settling times, etc.). In such manner, the plant-wide control of the entire process can be performed by setting targets and constraints on the flow rates and on the properties of material streams.

The plant-wide control scheme is implemented using iterative set-point optimization on the basis of the local models taking into account the dynamic behavior. When the local controllers are model-based, the response surfaces can be computed from these models. This is not the case, if classical control schemes are used, where they must be derived from empirical data.

## **2.4 Current and Future Requirements to Process Sensors**

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. 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. As a consequence, smart process sensors enable new business models for users, device manufacturers, and service providers.

Recently the technology roadmap "Process Sensors 4.0" was published [16], 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 include

- Connectivity and communication ability according to a unified protocol
- Maintenance and operating functions
- Traceability and compliance
- Virtual description to support a continuous engineering
- Interaction capability

These smart functions of sensors simplify their use and enable plug-and-play, even though they are more complex. This is particularly important for, self-diagnostics, self-calibration and self-configuration/parameterization.

The departure from current automation to smart sensor has already begun. Further development is based on the actual situation over several steps. Possible perspectives will be via additional communication channels to mobile devices, bidirectional communication, integration of the cloud and virtualization. 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.

Such powerful analytics will help optimize both assets and systems. Predictive analytics will be installed to reduce unplanned down-time. Newly available information generated by these tools will lead to new, transformative business models supported by new applications. Instead of offering physical products for sale, companies will increasingly offer products "as a service" – maybe also NMR instruments along with data analysis tools.

### 3 Compact NMR Spectroscopy in Process Control

Monitoring chemical reactions is the key to chemical process control. Today, mainly optical online methods are applied. As mentioned in the introduction, NMR spectroscopy has a high potential for direct loop process control. High-field NMR instruments give detailed structural information on chemical compounds and reactions. However, such instruments are somewhat expensive and complex to operate. On the contrary, low-field NMR instruments based on permanent magnets are robust and relatively inexpensive alternatives, which feature advantages like low cost, low maintenance, ease of use, and cryogen-free. While low-field NMR does not provide the detailed information provided by high-field instruments as a result of their smaller chemical shift dispersion – and sometimes complex secondary coupling – it is of practical value as a process analytical technology (PAT) tool. However, each of the conventional optical spectroscopic online methods is limited in scope and requires the analyte to exhibit specific features like absorption or scattering characteristic different from the solvent or matrix, optical transparency, low scattering of the matrix, or absence of particles or gas bubbles. Due to detection of functional groups, optical spectroscopy basically cannot provide structural details. NMR is unique as it requires no such features and can deliver both speciation and structural information providing a real advantage over optical techniques in terms of not requiring optical access and being readily applied to opaque samples.

Instruments for online NMR measurements with a flow-through cell, possessing a good signal-to-noise-ratio, sufficient robustness and enable integration into industrial plants (i.e., explosion safety and fully automated data analysis) are currently not available off the rack. Recently, promising benchtop NMR instruments with acceptable performance came to market (cf., 3.2 and 4.1), and process integrated sensors developed on basis of such laboratory instruments are on their way. Recently, reviews were published by Mitchell et al. [17], Zalesskiy et al. [18], and Dalitz et al. [19]. This review focuses on the most recently published work since 2012. First studies with this technology in the literature showed promising results from laboratory experiments (cf., 3.3 and 4.2).

#### 3.1 Quantitative NMR Spectroscopy of Technical Mixtures

NMR fundamentals with respect to industrial applications were recently presented in [20, 21]. Online applications of NMR spectroscopy involve a continuous circulation of a reaction mixture from a vessel through a flow cell within the NMR spectrometer, which is often part of a thermostated bypass setup (cf., 5, [22–24]). NMR spectra are recorded over the course of a reaction to monitor its progress, while providing quantitative as well as structural information on reactants, intermediates and contaminants.

In NMR spectroscopy, the signal area is directly proportional to the number of nuclei in the detection volume of the NMR instrument, therefore a relative quantification can be performed without the need of prior calibration. Another benefit is the high linearity of quantitative NMR spectroscopy, which stays valid even when big changes in sample matrix occur, e.g. over the course of a chemical reaction. According to this, absolute quantification can be achieved by adding a certain amount of a standard substance, comparable to a single point calibration. This often leads to problems because of the requirement of a stable, non-reactive compound, which has no influence on the reaction itself. Therefore external standards [25] or even virtual referencing methods like ERETIC (Electronic Reference to Access in Vivo Concentrations) were developed, which introduce a calibrated RF signal as a quantitative reference [26-30].

To ensure quantitative NMR conditions, which means that all components in the sample are determined with equal sensitivity, several prerequisites need to be considered. These can be either requirements applied to any quantitative NMR experiment or some special considerations applied to reaction mixtures in a flow setup. In high-resolution NMR spectroscopy the preparation procedure starts with tuning and matching of the RF (Radio Frequency) circuit after inserting the sample. For many compact NMR devices, this step can be skipped, because these properties are set to a fixed value suitable for most applications. This is followed by shimming, which represents the homogenization of the magnetic field within the sensitive region of the spectrometer. While early devices required time-consuming manual shimming, today nearly every spectrometer uses automatic algorithms based on a certain sample like H<sub>2</sub>O—D<sub>2</sub>O mixture. Zientek et al. showed that some automatic shimming routines are also applicable directly to the reaction mixture [31]. Field frequency lock based on deuterium signal is often not applicable in reaction monitoring, because of the application in the unmodified technical mixture without addition of deuterated substances. Modern superconducting magnets show good field stability, which allows unlocked measurements to be conducted over several hours. Some applications use external lock substances based on <sup>2</sup>H or <sup>19</sup>F mounted in the probe [32] and/or software-based drift-correction algorithms to overcome this problem.

To maintain quantitative conditions, several experimental parameters need to be set accurately. This contains for example the number of accumulated scans *nt* depending on the concentration of the reactants, as well as the desired time-resolution. The acquisition time *at*, which represents the time period for data acquisition of the FID shortly after excitation pulse, should be set accurately to avoid truncation of the FID leading to artefacts in the NMR spectrum. According to the position of signals for quantification adjustments in transmitter offset frequency *tof* and sweep width *sw* can be useful. To ensure uniform excitation of all nuclei in the sample sweep width should be slightly wider than the last occurring signal at each end of the spectrum. This can be adjusted by changing the excitation

profile via length of the broadband RF pulse. The most important parameter is the relaxation delay  $d1$  setting the time period between two acquisitions needed for sufficient relaxation of the nuclei. This is strongly dependent on the nucleus-specific property of longitudinal relaxation time  $T_1$  under reaction conditions.  $T_1$  can be determined prior to the measurement by using the inversion-recovery or saturation-recovery NMR experiment. The pulse repetition time, consisting of acquisition time  $at$  and relaxation delay  $d1$  should be at least  $5 \cdot T_1$  for a recovery of magnetization by 99.33 % [33]. This can be adjusted either by changing the flow rate of the sample within the NMR spectrometer, or by choosing a suitable relaxation delay  $d1$  for the nucleus with the longest value of  $T_1$ . When increasing the flow rate premagnetization should be considered to assure that every nucleus is experiencing equal magnetic field strength before excitation [34]. Alternatively, the signal areas can be corrected for relaxation issues when the relaxation rates of all compounds are known as these effects are strictly deterministic [24].

The software solutions of benchtop NMR vendors are often user-friendly control interfaces, allowing changes to a limited set of parameters only. For applications in process monitoring an extended accessibility of experimental parameters is desirable for adjustment to the specific requirements of the sample.

Solvent suppression techniques like PRESAT or WET (Water Suppression Enhanced through  $T_1$  Effects) are well established on high-field NMR instruments using presaturation or field gradients introduced by PFG (Pulsed Field Gradient) units [35-37]. Especially in reaction monitoring suppression of the solvent signal can help to achieve a significant increase in sensitivity, due to a better exploitation of the available range of the analogue-to-digital converter (ADC). To maintain quantitative conditions selective methods like WET are highly desirable on compact NMR devices. First gradient units developed for DOSY (Diffusion Ordered (NMR) Spectroscopy) applications are now available, but unfortunately barely any of the instrument vendors offer suitable hardware options enabling the user to apply solvent suppression [38].

Determination of signal areas can be performed with different methods after preprocessing consisting of phasing and baseline correction. While the classical approach of numerical integration over a certain multiple of line width is only suitable for clearly separated signals, complex spectra with signal overlaps often need more advanced approaches like line fitting or chemometric methods.

### 3.2 Compact NMR Spectroscopy Hardware Developments

Presently a number of benchtop nuclear magnetic resonance spectroscopy instruments are available. These instruments already exhibit exciting narrow lineshapes in spite of the major challenges for benchtop NMR spectrometers to generate of a stable and homogeneous magnetic field  $B_0$  in the

active volume of the probe, which is a big challenge for compact magnets while using less shim dimensions compared to high resolution spectroscopy. Field strengths are usually below 1.88 T (80 MHz proton frequency) for the observation of  $^1\text{H}$ . Presently also  $^{19}\text{F}$  and  $^{31}\text{P}$  nuclei are observable with such NMR instruments with acceptable sensitivity. For benchtop laboratory applications also  $^{13}\text{C}$  instruments are available, which are typically not appropriate for process control due to the long acquisition times needed.

### 3.2.1 Current Market Situation

Some of the companies offering NMR system are (in alphabetical order) ABQMR [39], Acquitex [40], Anasazi-Instruments [41], Bruker [42], CEM [43], COSA Xentaur [44], Cryogenic [45], HTS-110 [46], JEOL [47], Krohne [48], LexMar (former Progression) [49], Magritek [50], Modcon Systems (former Qualion) [51], MR Resources [52], Nanalysis [53], Niumag [54], One Resonance Sensors [55], Oxford Instruments [56], Process Control Technology [57], Process NMR Associates [58], Resonance Systems [59] and [60], SpinCore Technologies [61], Spinlock [62], Stelar [63], Tecmag [64], Thermo Fisher Scientific [65], Xigo Nanotools [66]. Very unfortunate for the community is the disappearance of Agilent (former Varian) [67] from the NMR market. However, a considerable number of instruments are still maintained.

### 3.2.2 Instrument Quality Assessment

Imperfections of the magnetic field homogeneity produce substantial broad signal fragments, which typically occur in the signal base. Thus, a significant part of the signal is captured in the broad base of the line, which reduces the signal-to-noise ratio and adds contribution from the background noise. This is a concern when quantitative NMR analysis is desired. Direct integration methods (e.g., integrating 64-fold signal half width) are hindered due to the reduced signal dispersion due to the lower magnetic fields, which also suffer severely from additional base-broadening. In addition, line fit methods become inaccurate when not using appropriate line fitting functions or an adequate number of functions.

The most common standard test procedure for characterization of resolution in high resolution NMR spectroscopy is the line shape test or so called hump test. Albeit the line shape test is principally appropriate for characterizing low-field NMR instruments, line widths at other signal heights than the conventional values at 50 %, 0.55 %, and 0.11% were reported in the literature or in instrument specifications such as, e.g., 50 %, 10 %, and 1 %, since the lowest values cannot be resolved due to reduced signal-to-noise ratio – or they look too bad. In addition, samples containing deuterated solvents are expensive and, thus, poorly manageable in open systems such as flow cells and periphery used for reaction monitoring. Although such specifications are precise and practical,

comparisons between various probes at different field strengths are obstructive and a commonly accepted instrument test is highly appreciated.

For a general performance characterization of low-field NMR instruments we propose a semi-empirical approach to obtain and evaluate the so-called instrumental function to judge on the instrument performance. The instrumental function is a characteristic function for a spectrometer which impacts the ideal spectrum. It can be achieved from experimental spectra of commonly available solvent (e.g., acetone, water, cyclohexane, etc.) by deconvolution of a given reference signal. Reference signals of ideal line shape can be selected according to the experimental requirements, e.g., using theoretical values or expected values derived from high resolution instruments. It came out that the line shape deconvolution method obtains information on the quality of a current lineshape and it hence is very helpful for method validation.

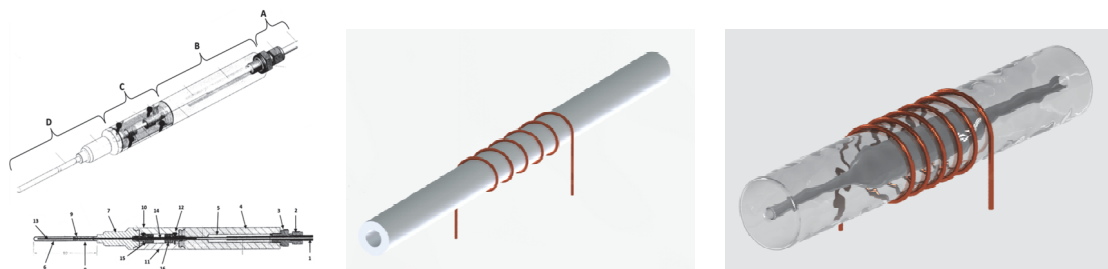
The NMR user should be aware of the contingency that "original data" of some manufacturers have somehow received internal editing such as remove of faster relaxing and hence distorted signal fragments at the cost of signal amplitude. Therefore any lineshape analysis only exhibit superficial results when it is not used in connection to the signal amplitude or the signal-to-noise error and sensitivity of that instrument as a critical quality attribute. The sensitivity of a spectrometer is typically determined from the signal-to-noise ratio of 1.0 wt.-% ethyl benzene in  $\text{CDCl}_3$  solution (and ideally – but not always – given after internal editing as aforementioned). Roughly such values compare to high-resolution sensitivities (if no radiation damping occurs) for identical active volumes, because S/N theoretically varies with  $B_0^{7/4}$ . [68]

An important task is to provide the highest possible S/N ratio in a flowing fluid especially at moderate flow rates. Considering typical longitudinal relaxation times of organic solvents in the order of 1–6 s plus the small inner diameters of the flow tubes suggest very low flow rates in order to fully develop thermal equilibrium magnetisation. For superconducting magnets a strong  $B_0$  stray field points into the direction of flow. Hence,  $B_0$  is early present for an inflowing sample. While for MR-NMR spectroscopy  $B_0$  is typically arranged perpendicular to the direction of flow and the stray field is much more compact compared to a superconducting magnet, one expects the premagnetization behavior to be more challenging with respect to the polarization length [19, 24, 69, 70]. The dynamic polarization behavior for neat ethanol at varying flow rates is shown in [68].

### 3.2.3 Principal Approaches towards Online NMR Flow Probes

Today, most compact NMR instruments are laboratory benchtop instruments, which accommodate standard 5 mm NMR tubes. The use of such NMR tubes as static rapid injection reactors is principally possible since reagents can be added outside the NMR instrument and inserted reasonably fast into the instrument to follow the subsequent reaction. [71] Since this approach lacks the control of real

reaction conditions as under technical condition, results are highly questionable. [72] This is mainly due to strong temperature gradients and reduced mixing in the NMR tube.



**Figure 2:** Three concepts for the realization of a NMR-flow-measuring cell. [69, 70] Left: 5 mm sample tube; middle: flow cell on basis of a 1/16" FEP line [68]; right: NMR-optimized Dewar glass cell, such as, e.g., described in [146].

Recently, a 5 mm NMR flow probe was described, which can be inserted into any instrument. Except the 5 mm glass tube itself, all connected tubing and junction can be liquid thermostated by a heating liquid (cf., **Fehler! Verweisquelle konnte nicht gefunden werden.** and, e.g., [73, 76]).

The use of commercially available poly fluorinated polymer lines (FEP: co-polymers from tetrafluormethylene/hexafluorpropylene, PTFE: polytetrafluorethylene, etc.) as an NMR flow cell as depicted in the middle of **Fehler! Verweisquelle konnte nicht gefunden werden.** offers a higher level of confidence to industrial users because the pressure resistant lines can be replaced end-to-end. Lines can be manufactured industrially precise and offer a high level of reliability, since they have a wide pressure, temperature and pH-range high stability. In that case, benchtop NMR development issues are the provision of a thermal isolation between the flow tube (i.e., the flowing process stream under given temperature, concentration, and pressure conditions) and the NMR instrument, e.g., by inserting a Dewar tube. [68] Several manufactures (to our knowledge, e.g., Bruker [42], JEOL [47], Magritek [50], or Thermo Fisher Scientific [65]) readily provide reaction monitoring sets, which are based on such a concept.

However, provision of the best possible signal-to-noise ratio in a flowing fluid, which is particularly difficult for low field NMR, requires design of an NMR-optimized flow cell. Only such concept, which are highly desirable offer the best possible results on NMR signal and dwell times for process control. An ideal flow cell is also schematically depicted in **Figure 2**.

### 3.3 Application of Compact NMR Spectroscopy for Process Control

Recently, the number of publications and conference papers on reaction monitoring with NMR spectroscopy is increasingly growing. Among these contributions, a focus can be found on pharmaceutical development, such as monitoring dissolution of pharmaceutical formulations [75,



76], based on work by Khajeh et al. [77]. Foley et al. showed that NMR spectroscopy is a valuable analytical tool among others for development of pharmaceutical active ingredients (APIs) [74, 78, 79]. NMR spectroscopy has also been applied for dissolved hydrogen [80] or by use of  $^{31}\text{P}$  NMR spectroscopy [81]. Benchtop NMR instruments in the fume hood were very recently described for various reaction monitoring applications [31, 68, 82–84, 147]. Since the purchase of compact NMR spectrometers is moderate, they are also increasingly used in education [85, 86].

Time-resolved or fast acquisition techniques comprising new methods have become progressively more important. [38, 87, 88] These experiments benefit from pulsed field gradients, which are also still missing as commercially available equipment. Further miniaturization of instruments is also ongoing. [89]

### 3.4 Automated Data Pretreatment and Evaluation

For reaction monitoring and process control using NMR instruments, in particular, after acquisition of the FID the data needs to be corrected in real-time for common effects using fast interfaces and automated methods. Conventionally, sensors have to be calibrated in a first step to find a response curve between the sensor signal and physical or chemical properties of the sample. In a second step, a model of the response between these parameters (e.g., concentrations) and the targeted quality specifications is needed. Thanks to the direct proportionality of the molar concentrations and the NMR signal, it could directly be used in the near future to relate the process target quality specification to sensor data – also in combination with multiple other sensor or process information.

#### 3.4.1 Data Processing

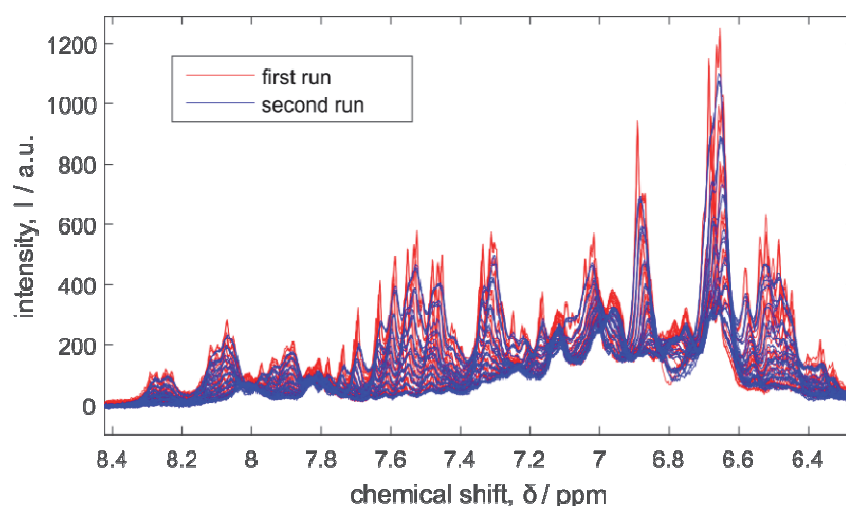
In order to remove small magnetic field drifts the Fourier transformed spectrum has to be phased, baseline corrected and aligned to a dominant signal in the technical sample with only a minimum amount of user interaction [90]. Moreover, automatic data processing circumvents the error that is introduced by the user in manual data processing. A series of data processing methods that work unsupervised have been reported recently and the source codes are partially accessible [91–94].

**Minimum Entropy Phase Correction.** This phase correction algorithm was originally published by Chen and co-workers [94] and MATLAB source code is available free of charge. The algorithm corrects the zero and first order phase by minimizing the entropy using non negative signals as a constraint. The algorithm works with no user interaction and has been already used for batch data processing of NMR experiments [31, 68]. To improve the result the method can be modified so that it works selectively in predefined spectral regions and leave out noisy regions, or regions with artefacts, e.g., from WET solvent suppression. Various automated phase correction algorithms were compared in the literature [95].

### 3.4.2 Methodologies for Data Evaluation and Modeling

One of the fundamental acceptance criteria for online NMR spectroscopy is a robust data pretreatment and evaluation strategy in order to gain long-term reproducibility under varying process conditions. The online spectra of different batches with the same set-up can vary due to the quality of the respective shim, prohibiting the use of identical automated data processing.

**Practical challenges.** An example using a compact NMR instrument (43.5 MHz) shows this fact, where the processed online spectra (automated baseline correction and phasing) of the coupling of two aromatic substances in a lithiation reaction for two identical batches are compared in the aromatic region (**Figure 3**). These deviations can either be minimized by sophisticated data preparation methods, which bear the risk of losing important structural information, or have to be taken into account for the choice of data evaluation method. For evaluation of spectral NMR data a broad range of methods are available.



**Figure 3:** Preprocessed  $^1\text{H}$  spectra at 43 MHz for two batches of a lithiation reaction using 1-Fluoro-2-nitrobenzene, Lithiumbis(trimethylsilyl)amide, and 2-Nitrodiphenylamine.

**Integration Method.** Direct Integration is the method of choice if peaks do not overlap, are well resolved and the baseline is stable. In the case of overlapping peaks line fitting (LF) with Lorentzian-Gaussian functions can be used to convolute spectra. Even for complex spectra Global Spectrum Deconvolution (GSD) was successfully applied for high field NMR data in order to providing automated full peak information in the spectrum [96].

When it comes to data evaluation under industrial process conditions in technical mixtures, the shape of signals can change drastically due to nonlinear effects. Additionally, the multiplet structure becomes more dominant because of the comparably low-field strengths in compact NMR which results in overlapping of multiple signals. For the described field of application the researcher is faced

with many variables and relationships, and the objective is merely to construct a reproducible and robust predictive model. Therefore multivariate data analysis is a promising tool.

**Multivariate Analysis.** Multivariate models are built with a suitable training data set, which are pretreated in the same manner as the process spectra. The training data set can be obtained from a set of spectra with a known composition or directly from process spectra and reliable data from a reference analysis. Partial least square regression (PLSR) and Indirect Hard Modelling (IHM) are two prominent examples for this model based evaluation.

**Calibration.** NMR spectroscopy is basically calibration free, since all nuclei of a certain isotope have the same sensitivity and NMR spectroscopy is linear over the whole concentration scale. In some cases for example the set-up and training multivariate models calibration is also necessary for NMR applications. There are two types of calibration methods, offline calibration and in-process calibration. The first method uses a set of gravimetrically standards the later uses spectra from samples that are directly obtained from the sample and analyzed by a suitable reference analysis. For a robust model the composition of the samples need to cover the whole design space and therefore the reference samples are planned by a Design of Experiments (DoE) [97]. With the concept of DoE a maximum of information can be obtained with a minimum amount of samples [98].

**Partial Least Squares Regression (PLS-R).** For industrial applications, partial least squares regression is a popular method for soft modelling. PLS-R performs a data reduction for functionally correlated data by finding factors in the NMR spectra ( $\mathbf{X}$ ) that are also relevant for the quantity of reactants ( $\mathbf{Y}$ ). This is realized by determining a set of latent variables that perform a simultaneous decomposition of  $\mathbf{X}$  and  $\mathbf{Y}$  with the constraint that these components explain as much as possible of the covariance between  $\mathbf{X}$  and  $\mathbf{Y}$ . Since PLS-R is an inherent linear method, additional latent vectors are needed to model nonlinear effects, including peak shifts or deviation of line shapes which are typical for NMR spectra. In principle, Multiple Linear Regression (MLR) can be used with very many factors. However, if the number of factors gets too large a model will be generated that fits the sampled data perfectly but will fail to predict new process data well (over-fitting). In order to compensate for variations in spectra binning is applied conventionally [99-101]. With recent improvements in software, spectral alignment is now starting to replace the need for spectral binning [92, 102]. In contrast to IHM extrapolation should be avoided since the established relationship between  $\mathbf{X}$  and  $\mathbf{Y}$  is only supported in a region close to the calibration points [98].

**Indirect Hard Modeling (IHM).** IHM uses a mechanistic model (hard model) of pure component spectra based on first principles of spectroscopy. These hard models consist of a sum of Lorentz-Gauss functions, which represent the peaks in the pure component spectrum. The model resembles the peaks using the Lorentz-Gauss parameters that can be referred to physical properties like peak

position and concentrations. The spectrum of a mixture can be composed using a weighted sum of various hard models. While the component weight parameters are correlated with the component concentrations, the peak parameters are used to describe the shape of the spectrum. Peak shape variations in the measured spectrum, e.g., due to shifting peaks or changing susceptibility, can be accounted for by an automated adjustment of the corresponding peak parameters within predefined limits, thus reducing error propagation to the relevant component weights. In contrast to most other methods, the model is capable of extrapolation, as the component weights are robust against shape changes and highly selective for a certain component. The creation of the hard model as well as fitting the hard model to mixture spectra in order to adjust peak parameters and obtain component weights are fully automated [103, 104] and implemented in commercially available software [105]. Its applicability for compact NMR spectra has been already reported [31].

## 4 Compact Time Domain NMR in Process Control

Apart from the spectroscopic approach of compact NMR in process control discussed so far, imaging and time domain NMR are well known and established also in the industrial context. On the basis of the substance specific NMR relaxation rates, differentiation and quantification of components also in complex materials was achieved already in the early days of compact NMR. Additionally, diffusion properties can be exploited in the context of product control, mainly either as diffusion weighing to suppress for example the fast diffusing moieties in the sample [106-108] or to get structural information via hindered or restricted diffusion [109, 110]. It should be mentioned that correlations between relaxation rates or between relaxation and diffusion can be measured and explored to get more detailed insight into sample composition [111, 112]. A variety of application fields is established also in industrial environments, ranging from polymer or food characterization to quality control of various products. In industrial process control, most often dedicated instrumentation is used, which is combined with optimized pulse sequences and data processing schemes. Common to all these approaches is the fact that the NMR signal is acquired in the time domain and no chemical shift dispersion is required to answer questions of quality and process control.

### 4.1 Time Domain NMR Approaches

Commonly,  $^1\text{H}$  NMR as the most sensitive and widely applicable modality is used in process control by compact NMR. Robustness, interdependent of environment parameters, high stability, reproducibility and inexpensiveness are mandatory. Amongst the NMR methods, relaxometry and diffusion measurements are the most easily achieved. Diffusion measurements are most often performed applying pulsed field gradient echo sequences. The homonuclear dipolar interaction dominates the  $^1\text{H}$ -NMR relaxation in soft matter, such that these parameters are in focus. The

transverse relaxation rate is especially sensitive to fluctuations of this interaction in the low frequency range of kHz, whereas the longitudinal relaxation indicates mostly fluctuations in the range of the Larmor frequency in the MHz range. Other material specific time constants like the relaxation rates in the rotating frame, the dipolar relaxation or the multiple quantum build-up are known, being exploited to differentiate either different materials or to determine the state of the substance under investigation.

For robust and fast while accurate measurements in quality or process control, dedicated time domain NMR sequences were developed with the aim of maximum sensitivity towards the property to be characterized. In former times, the timing of a conventional NMR sequence like a Hahn-echo was optimized and specified. Meanwhile, specific pulse sequences were established for these purposes like combined relaxation [113, 114] or diffusion weighted sequences.

Data acquired via these dedicated sequences usually afford special data treatments as the analytical description is often hampered. Often, signals cannot unambiguously be assigned to a specific component in the sample under investigation. Multivariate approaches [115, 116] are known as well as dedicated procedures [117, 118] and numerical approaches like inverse Laplace transform [116, 119]. A recent review concerns these aspects as well as hardware aspects in more detail [17]. It should be mentioned that several attempts are currently in progress to build smaller and cheaper compact NMR instruments while keeping the flexibility along the lines in reference [18].

## 4.2 Field Applications of Time Domain NMR

**Moving samples.** In process and quality control, often moving samples are involved, for example samples on a conveyor belt or a liquid in a pipe. While liquids allow direct analytical access to mechanic properties like viscosity and reaction monitoring in a bypass via spectroscopy or relaxation [120-123], discrete samples might be investigated directly [124] or via continuous wave free precession (CWFP) techniques [125].

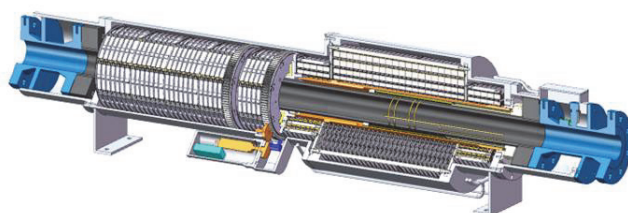
**Food processing.** The classic field of application of compact NMR also with respect to quality and process control is food processing and industry. As relaxation and diffusion properties are well suited and relatively easily addressable by means of the NMR methods established in compact NMR, several studies address the question of measuring through packaging especially with the aim of contactless quality control of the final product. Although this idea lead several developments in the past already, the newer studies reveal the current interest and progress [126, 127].

**Polymers and composite materials.** A third application field to be mentioned concerns polymers and composite materials. Especially field cycling and compact NMR relaxometry are applied to study the quality of materials via molecular dynamics. The single or multiple quantum magnetization build-up

curves as well as the decay curves are often described by more or less empirical equations [128-130, 148, 149]. Correlations to results of other analytical modalities sometimes result in characteristic numbers which are well suited for quality control. Single sided NMR might be used as a suitable tool in quality control of almost arbitrarily shaped end products or during processes when the fundamental questions are answered and correlations with material properties are established.

**Petrol and oil industry.** An evolving field of application of compact NMR can be seen in petrol and oil industry. New NMR dedicated sequences and data processing strategies are evolving for example to quantitatively differentiate oil and brine [108] or to measure asphaltenes [131] as precursors for product and process control. As a part of this field, a large number of investigations of biodiesel and related substances can be found, which explore the use of relaxometry for quality and process control [132-134]. It is essential to prove the measurement and processing strategies in lab scale experiments while knowing the physico-chemical details of the process in order to optimize the application with respect of measurement time, accuracy, reproducibility and clearness.

Time domain NMR can also be applied in the upstream oil and gas industry to measure multiphase flow of oil—water—gas mixtures upstream of a separator. To this end, an industrial magnetic resonance multiphase flowmeter has been developed [48, 135]. After the successful tests on various multiphase test loops, the magnetic resonance multiphase flowmeter has been installed in a field trial by a Dutch exploration and production company on a production location in the Netherlands. It was commercially released in 2015.



**Figure 4:** Simplified drawing of the magnetic resonance multiphase flow meter. The flow meter comprises two major components: the pre-magnetization section on the left hand side as well as the measurement section on the right hand side.

The flow meter comprises two major components: a pre-magnetization section featuring three magnet segments, which can individually switched off by turning parts of the permanent magnets and a perturbation and measurement section involving a radio-frequency coil (**Figure 4**). A strong contrast can be created between the signals originating from oil and from water based on the difference in  $T_1$  times by varying the pre-magnetization length. It was also shown that the sensitivity

of the NMR flow meter for determining the water liquid ratio increases with increasing water liquid ratio, demonstrated by an increased separation of the water liquid ratio lines with increasing water liquid ratio. This method remains robust even when phase slip between the oil and water phases is present. The instrument eliminates expensive oil—water—gas phase separators in the field in combination with individual analytical instrumentation for the three phases and individual flow metering units. Analogously, very low earth magnetic fields can be used making the technique potentially more flexible [143].

**Oilfield emulsions.** Water-in-crude oil emulsions are prevalent in the global petroleum industry and can form during crude oil production as fluids are transported through various high shear regions (e.g., valves, chokes, and pumps). Recent process NMR applications, e.g., can be found in [137-140]. NMR measurements are challenging because the NMR signal from the oil phase erroneously contributes to the measured water droplet size distribution.

## 5 Field Integration

### 5.1 Sampling

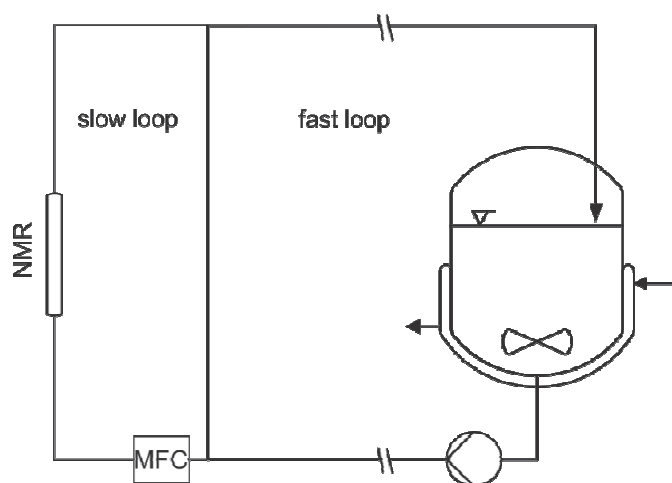
Like in any analytical method, sampling is a crucial step for getting reliable data with high quality. In the case of field integration, online setups represent the most convenient type of sampling in field application, because of the ability to maintain process conditions over the whole way from the reactor or tubing to the NMR spectrometer. Therefore it is important to provide suitable equipment like thermostated and, dependent on the conditions, pressure-resistant sample lines and flow cells. After passing the spectrometer the sample can either go to waste or due to the non-invasive measurement of NMR be recycled to the process without loss of quality. In contrast to at-line techniques like most chromatography process applications the sampling step is fully automated and the system doesn't need any intervention of the plant operating personnel. This goes along with a significant saving in costs and increasing of safety because no manual sampling at the plant setup is required.

The implementation of a process analytical device like an NMR spectrometer should be always in close cooperation of PAT specialists and process engineers on-site to ensure the best position for obtaining accurate results concerning the desired task. Constraints like sediment loading or gas bubbles in the reaction mixture should be considered by integration of suitable separators like filters or changing the position of the device to ensure a homogeneous flow. Sample lines should be planned as short as possible to reduce delay times and facilitate preservation of the process conditions. The small dimensions of compact NMR instruments in combination with robustness against external influences make them suitable for implementation in a rough industrial

environment. In accordance with relevant regulations it can be even applicable within an explosive hazardous area by using suitable concepts and equipment (cf. 5.4).

## 5.2 Bypass

Online NMR systems are usually integrated using a bypass setup with direct connection to a chemical reactor or part of the related tubing system. Depending on the process conditions and the sampling position pressure differences in the plant can be exploited or an external pump is required for providing the flow of the reaction mixture through the system. The flow system is often divided in two loops with a high and a lower flow rate, respectively (**Fehler! Verweisquelle konnte nicht gefunden werden.**). Valves can be used for splitting the flow to reduce dead times, while at the same time ensure quantitative flow conditions within the NMR spectrometer. In more complex applications with high potential of changes in physical properties like density and viscosity of the flowing sample, application of a mass flow controller (MFC) instead of simple split valves might be useful to ensure invariant flow conditions. Depending on the properties of the reaction mixture, as well as the process conditions different tubing material can be used for flow setups, including high-performance or fluorinated polymers like PEEK or PFA, as well as stainless steel. While most of the NMR instruments use flow cells with 5 mm outer diameter convenient tubing dimensions are in the range of 1/16" to 1/8". Typically used types of connectors reach from HPLC fittings in application labs up to industry approved clamping ring connections or even welded lines in a plant environment.



**Figure 5:** Bypass setup with fast and slow sample loop for integration of online NMR instruments driven by a pump (MFC = mass flow controller)

## 5.3 Explosion Protection

In order to integrate compact NMR spectrometers into the real process environment special attention has to be paid to explosion protection guidelines, since the majority of commercial available instruments come without explosion protection (cf., 3.2.1). The requirements for electrical

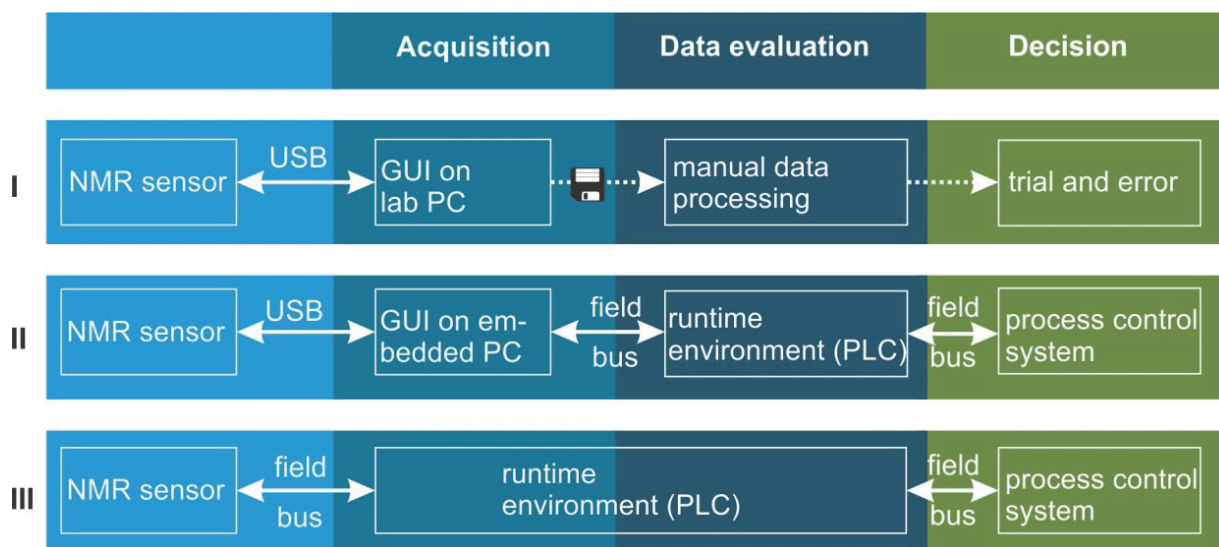


equipment and protective systems for use in hazardous areas are described amongst others by ATEX (European guideline 94/9/EC [141]) or by IECEx (international commission system for certification [142]). Depending on the type of materials that arise in the process, the frequency and duration of the occurrence of these materials, different protective requirements arise. Therefore, areas subject to explosion are divided into 6 different danger zones, according to CENELEC (European Committee for Electrotechnical Standardization) and IEC (International Electrotechnical Commission). 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., pressurized enclosure or flameproof enclosure, can be implemented. In addition, components for automation (e.g., embedded PC: Personal Computer, PLC: Programmable Logic Controller) have to be integrated into the explosion protecting concept and connected to the spectrometer housing by appropriate data interfaces (cf., 5.4). Lastly, it has to be kept in mind to remove the heat accumulated in the explosion proof housing, in order to keep the magnet of the NMR instrument at constant temperature.

#### 5.4 Field Communication

At present, applications in literature show setups for process monitoring with NMR using a personal computer with a graphical user interface (GUI) for the method selection and acquisition of online spectra (cf., 3.3). In a second step, the data is manually evaluated (off-line) and compared to former results (**Figure 6–I**). Recently, as mentioned in chapter 2.3 engraving changes take place in information and communication technology and holds great opportunities for model-based process control with interconnected communicating sensors.

The transfer of firmware data from the instrument can be realized directly via an embedded personal computer for DIN rail systems (**Figure 6– II**) or via an external interface in the interest of virtualizing the instrument (**Figure 6– III**). By using a runtime environment, which can be implemented in a programmable logic controller (PLC), the method selection, acquisition, and data evaluation is performed online in a very stable system. However, due to the fact, that most of the recent commercially available benchtop spectrometer can only be accessed via its proprietary software on a windows PC an embedded PC close to the spectrometer has to be integrated into a process environment (**Figure 6– II**). For the future it is beneficial to establish a standard for exchange of data, e.g., OPC-UA [143], for the various signal processing steps as described in chapter 3.4. In that matter, signal processing can be carried out modular by the application of different software tools without compatibility problems. Yet, no standard interfaces are defined or implemented by the manufacturers.



**Figure 6:** Data flow chart for reaction monitoring in recent laboratory applications (I) and for process control (II and III).

## 6 Conclusion

Quantitative online NMR spectroscopy extends the tool box of established process analytical technology methods such as optical process spectroscopy. In particular structural and quantitative information are directly accessible from the spectrum and is linear in the entire concentration range. It can be used online in a wide temperature and pressure range for reacting technical samples without the need for deuterated solvents. An increasing number of examples underpin the practical applicability of the method. Effects arising from flowing samples (equilibria magnetization), the bypass setup (RTD), and from the design of the flow cell have to be taken into account under certain circumstances. Especially for benchtop spectrometer “easy to carry” experiments can be employed using commercially available 5 mm NMR probes or custom designed Dewar tubes and flow cells made from FEP or PTFE tubing.

Since reaction monitoring applications generate large amounts of data, modular data processing scripts or plug-ins together with commercially available vendor independent evaluation software faces these obstacles progressively. While evaluation methods like direct integration and line fitting are established methods in most software, distinct multivariate methods like PLS-R or IHM that handle evaluation of mixture spectra and above all non-linear effects (e.g., peak shifts and line broadening) are not yet employed and frequently used.

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