

Online NMR spectroscopy empowered by Indirect Hard Modeling

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Introduction

Nuclear magnetic resonance (NMR) spectroscopy is an emerging process analytical technique. High-field NMR spectroscopy is widely applied in lab environments, whereas the medium-resolution (MR) technique is beneficial in field use due to various issues:

- Lower stray fields
- Compact equipment (benchtop size)
- Permanent magnets without maintenance
- Lower acquisition and maintenance costs

For these reasons, the potential of MR-NMR for automated online analyses has been explored for a well-characterised esterification reaction.

In order to benefit from both versatility of proton (^1H) and specificity of fluorine (^{19}F) NMR spectroscopy, partially fluorinated substrates have been utilised.

Measurements

MR-NMR measurements were performed in a Spinsolve benchtop instrument (Magritek) (Figure 1) equipped with a 1/16" polymer tube as a flow cell, supported by a 5 mm glass Dewar tube. Resulting resonance frequencies were 43 and 40 MHz for ^1H and ^{19}F , respectively. A 500 MHz Varian (Agilent)

high-resolution NMR spectrometer was used as a reference (Figure 2).

Some premises were taken in order to allow comparability of medium- and high-resolution measurements, including back pressure control and precise determination of residence times in the transfer lines.

Measurement parameters are compared in Table 1.

The medium-resolution spectra from a reactive experiment show a reasonable signal dispersion and allow process monitoring already at first glance (Figure 3).

Quantitative analysis

Four methods for a quantitative analysis of the medium-resolution spectra were benchmarked with the highly resolved spectra:

- 1) Direct integration of characteristic signals
 - integration range: 64-fold half-width (FWHM)
- 2) Line fitting of characteristic signals
 - Gaussian-Lorentzian peak shape
- 3) Indirect Hard Modeling (IHM)
 - component models extracted from mixtures
- 4) Partial Least Squares Regression (PLS-R)



Fig. 1: Magritek Spinsolve benchtop NMR spectrometer.

All methods required data pre-treatment, including:

- Fourier transformation of the FID
- Baseline correction (3rd order polynomial)
- Phase correction by entropy minimisation
- Peak alignment (required for PLS-R)

Whereas direct integration and line fitting deliver results based on single peaks only, the IHM approach involves redundant peak information which helps to further improve predictions. In the presented sample reaction, a joint Hard Model is built for ^1H and ^{19}F spectra (Figure 4).

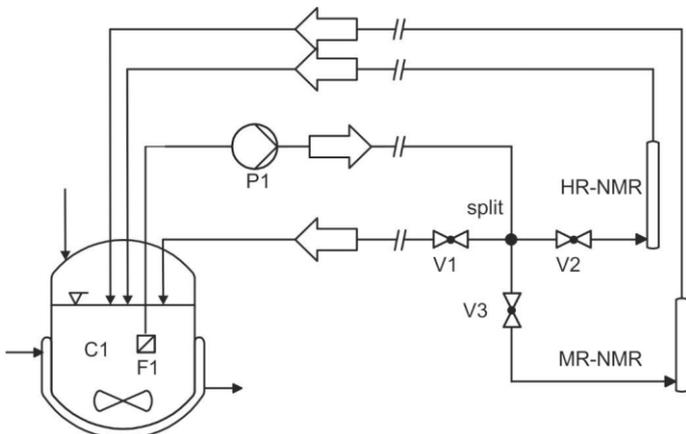


Fig. 2: Flow scheme of the HR- and MR-NMR setup.

Table 1: Parameters for MR- and HR measurements.

	MR-NMR	HR-NMR
Working frequency	43 (^1H), 40 (^{19}F)	500 (^1H only)
Flow rate range [mL]	0.1 – 0.5	0.1 – 1.5
Flow cell ID / OD [mm]	1.6 / 1.02	4.2 / 3.4
Sampling interval	(0.5 –) 1	(0.25 –) 1
No. of co-added scans	1	1

Combining both spectra in a single IHM model results in the following workflow for the analysis step:

- 1) Achieve separation of TFA and TFEA from ^{19}F .
- 2) Use 1.) to separate overlapping CH_2 signals of TFA and TFEA in the proton spectrum.
- 3) Assign CH_3 contribution of TFEA.
- 4) Identify remaining CH_3 signal and assign to AA.

Predicted profiles from an experiment confirm that the simultaneous analysis of redundant data increases the robustness of quantification (Figure 5).

Discussion

The prediction quality of the methods differs significantly (Table 2). Overall, PLS achieves better RMSEs than the univariate methods, if applied to the ^1H -NMR spectra only. The combined IHM performs best for AA and TFEA and is superior to the other methods for these two components. This indicates the high potential of the method, if partially redundant information is required and available.

As a measure of method robustness, the variance of predicted values from a typical steady state is calculated. Interestingly, IHM is able to maintain a reasonably low level when combining ^1H and ^{19}F spectra.

Acknowledgments

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Further reading:

N. Zientek, M. Maiwald et al., *Magnetic Resonance in Chemistry* **2015**, DOI: [10.1002/mrc.4216](https://doi.org/10.1002/mrc.4216)

N. Zientek, M. Maiwald et al., *Journal of Magnetic Resonance* **2014**, 249, 53 – 62. DOI: [10.1016/j.jmr.2014.10.007](https://doi.org/10.1016/j.jmr.2014.10.007)

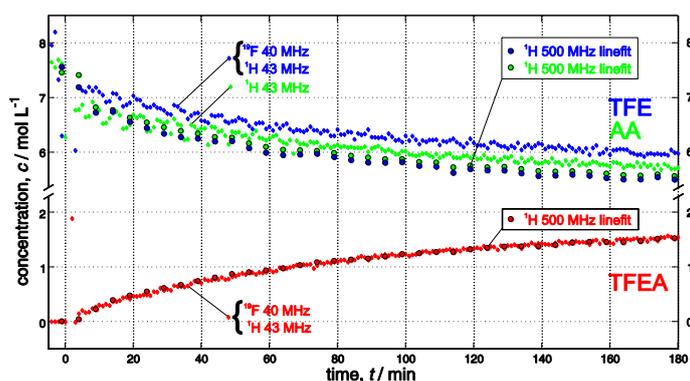


Fig. 5: IHM prediction for an esterification (MR-NMR).

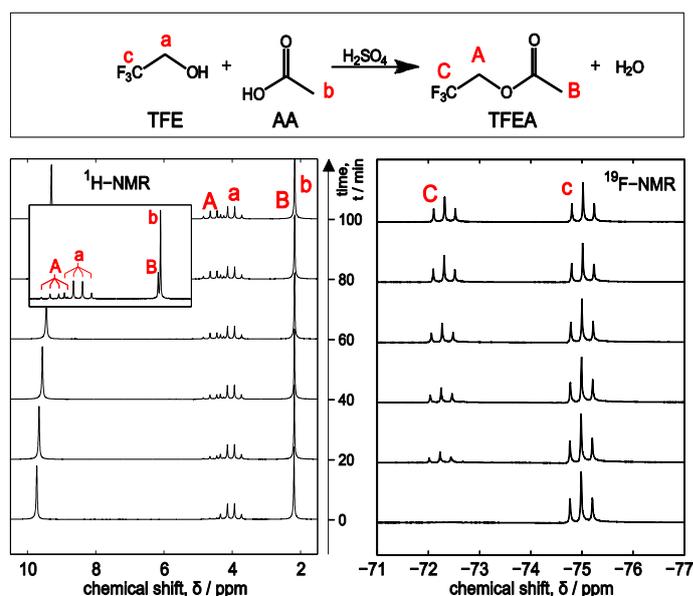


Fig. 3: Time series of MR-NMR spectra for esterification. Left: proton spectra, right: fluorine spectra.

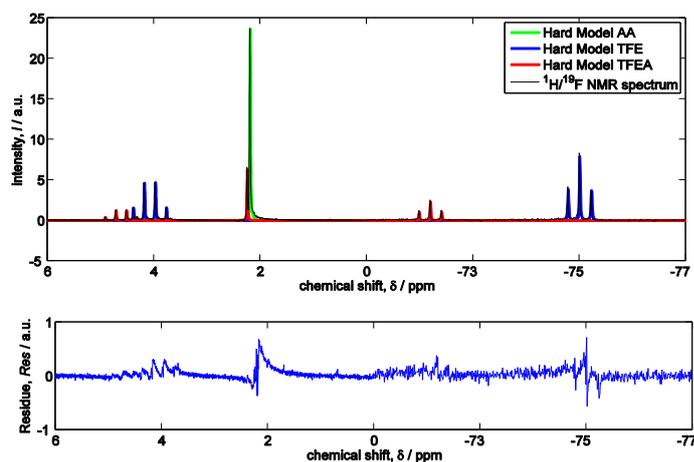


Fig. 4: Mixture Hard Model for the esterification reaction. 10 to 0 ppm: ^1H region, 0 to -200 ppm: ^{19}F region.

Table 2: Performance of methods (in mol L^{-1}).

	Integr.	Line Fit	PLS-R	IHM	IHM ($^1\text{H} - ^{19}\text{F}$)
TFE error*	0.19 ^H 0.29 ^F	0.15 ^H 0.62 ^F	0.058 ^H 0.70 ^F	0.16 ^H 0.52 ^F	0.46
AA error*	0.14 ^H	0.11 ^H	0.061 ^H	0.075 ^H	0.035
TFEA error*	0.18 ^H 0.17 ^F	0.26 ^H 0.25 ^F	0.11 ^H 0.17 ^F	0.17 ^H 0.28 ^F	0.14
Final precision#	0.047 ^H 0.23 ^F	0.031 ^H 0.36 ^F	0.025 ^H 0.11 ^F	0.038 ^H 0.076 ^F	0.037

* RMSECV, root mean square error of cross-validation.

Average of all available components.