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Nourhan Abouelell

Karlsruhe Institute of Technology

Junlin Liu

Karlsruhe Institute of Technology

Dominique Buyens

Karlsruhe Institute of Technology

Mengjia He

Karlsruhe Institute of Technology

Dmitrii Zasukhin

Karlsruhe Institute of Technology

Benno Meier

Karlsruhe Institute of Technology

Mazin Jouda

Karlsruhe Institute of Technology

Jan Korvink

`jan.korvink@kit.edu`

Karlsruhe Institute of Technology

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CMOS-Based Multiplexed NMR Acquisition toward High-Throughput Spectroscopy

Nourhan Abouelell¹, Junlin Liu¹, Dominique Buyens¹, Mengjia He¹, Dmitrii Zasukhin², Benno Meier², Mazin Jouda^{1,*}, and Jan G. Korvink^{1,*}

¹Institute of Microstructure Technology (IMT), Karlsruhe Institute of Technology, Karlsruhe, Germany

²Institute of Biological Interfaces 4 (IBG-4), Karlsruhe Institute of Technology, Karlsruhe, Germany

*mazin.jouda@kit.edu

*jan.korvink@kit.edu

ABSTRACT

An ongoing demand for high-throughput nuclear magnetic resonance (NMR) spectroscopy is driven by the need to push the limits beyond time-consuming analytics, offering researchers an accelerated method for, e.g., composition analysis and concentration determination for a large set of samples. The main technical bottleneck involves the simultaneous acquisition of multiple NMR free induction decay (FID) signals, and then efficiently relaying them for post-processing. The aim of this paper is to establish a method to overcome the cost and complexity of current parallel detection setups, which require multiple RF receiver ports and space crowding cables for each sample detection site. This work presents an application-specific integrated circuit (ASIC) (chip size $\approx 3 \text{ mm} \times 4 \text{ mm}$) fabricated using 350 nm CMOS technology to simultaneously acquire NMR signals from four different samples, thereby reducing the cost and complexity of the parallel NMR hardware by a factor of 4. A practical experiment is presented to show the multiplexing of four different NMR FID signals, acquired using a parallel four-detector NMR probe from Voxalytic GmbH, in a 11.74 T NMR magnet from Bruker (500.13 MHz ^1H Larmor frequency). Detectors 1 and 2 were configured for ^1H and ^{13}C , while detectors 3 and 4 for ^{19}F and ^{13}C . The acquired spectra confirmed the ability to multiplex NMR FID signals and efficiently transmit them over a shared cable, which is essential for high-throughput NMR spectroscopy in metabolomics workflows and drug discovery. Using the multiplexed acquisition scheme introduced a channel-dependent degradation in the linear amplitude SNR, ranging from 7.81 % to 32.12 %. A 32-scan averaging scheme was implemented which yielded SNR enhancement factors in the range of 5.01 to 5.31, approaching the theoretical limit of $\sqrt{32} \approx 5.66$. The second experiment deployed a single-sample Bruker broadband probe equipped with a dual-coil configuration, utilized on a 9.4 T NMR magnet (400.2 MHz ^1H Larmor frequency). The outer coil was optimized for ^1H and the inner coil for ^{13}C . For multiplexed acquisition, minor linear amplitude SNR degradations were introduced of 8.65 % for ^1H and 2.34 % for ^{13}C . Subsequent 16-scan averaging provided SNR enhancement factors of 3.99 and 3.88, respectively, approaching the theoretical limit of $\sqrt{16} = 4$. The results demonstrated the flexibility of the ASIC chip across a wide frequency range, enabling multi-nucleus acquisition of diverse isotopes. Furthermore, the system showed a long-term performance stability, making it suitable for multi-pulse sequences such as nutation and averaging experiments.

Introduction

High-throughput analytical workflows are essential in chemical screening, pharmaceutical drug discovery, and metabolomics^{1, 2, 3}. Nuclear magnetic resonance (NMR) spectroscopy is well suited to these applications because it provides detailed information on molecular structure, dynamics, and intermolecular interactions while preserving intact molecular systems⁴. NMR spectroscopy requires minimal sample preparation and is inherently non-destructive, allowing samples to remain chemically and physically intact for subsequent analyses. In contrast, mass spectrometry relies on ionization and often requires sample preparation steps, such as fragmentation or gas chromatography, which may partially or completely alter the original sample⁵.

A current challenge for NMR spectroscopy is sample throughput. A typical NMR instrument is based on one sequential sample at a time for analysis, for example focusing on a single active NMR nucleus like ^1H , ^{19}F , ^{13}C , ... and their couplings. Yet with the objective of efficient and proper structural analysis of families of compounds, parallel NMR experiments are mandatory for analyzing different samples taken from a large cohort^{6, 7}. Instead of a separate analysis of every sample, which is time-consuming, a parallel experiment is possible using a broadband probe. Additionally, a parallel experiment provides an interpretable and reliable multidimensional NMR technique⁸. Along with commercial broadband and multi-detector probes, extensive research in this sector is underway. The main concept involves multiple radiofrequency receivers, where each receiver is designed to detect the free induction decay (FID) signal of a specific nucleus. A common factor is that, for each nucleus, a

separate RF receiver port is required, which implies the need to purchase a multi-channel NMR console.

Another perspective to improve the throughput of NMR spectroscopy, is to design a probe with multiple RF detectors^{9, 10, 11}. Such a probe provides the ability to analyze different samples, which are physically separated, simultaneously. This approach is beneficial for any applications, such as drug discovery, involving a large number of compounds^{12, 13, 14}. Similarly, running a parallel NMR experiment dedicates at least two separated RF ports per detector, and consequently, the purchase of a multi-channel NMR console is mandatory. Furthermore, increasing the number of detectors can easily exceed the current commercial availability. Designing a probe with a higher number of detectors is challenging due to increased crosstalk and noise from large cable bundles, added to which the spatial constraints of the probehead shaft impose significant limitations on further increasing the detector density.

This paper presents our multiplexing concept, with, at its core, a custom multiplexing signal processing chip made in complementary metal oxide semiconductor (CMOS) technology. The embedding printed circuit board (PCB) provides the ability to simultaneously connect up to eight radiofrequency signal lines, and combine them into a single signal transmitted over one RF port, thus bypassing a multi-channel NMR console. The concept was verified by two experiments. To evaluate the proposed method under realistic experimental conditions, measurements were performed using Voxalytic parallel NMR probe. Four distinct samples were simultaneously scanned and then combined into a single RF signal. For the second experiment, a one sample custom broadband probe was mounted in a NMR magnet. The FIDs from two distinct nuclei in the same molecule were simultaneously acquired in parallel and combined into single signal. A discussion of the results from the two experiments, and an outlook on future work, is also included.

Experimental apparatus and methods

Experiment (1): System Design and Multiplexing Concept

In this section, a detailed overview of system design is described and detailed in Fig. 1. The Voxalytic parallel NMR probe was mounted in a 11.74 T NMR magnet. Although each detector was doubly resonant, our experiments only considered their primary RF channels. For the multiplexing experiment, the first and second detectors' primary channels were tuned for ^1H , and the third and fourth detectors for ^{19}F . The parallel probe was essential for the measurement, separately acquiring from four different samples simultaneously. Microfluidic tubes were connected to the inlets and outlets of the four detectors and allowed sample access from outside the magnet bore. The samples were loaded into the detectors using syringe pumps. The first sample was prepared as a ratio of 75 % Isopropanol, 20 % D_2O and 5 % of 0.1 M TSP solution. Similarly, a sample of 75 % Methanol, 20 % D_2O and 5 % of 0.1 M TSP solution was loaded to the second detector. For the third detector, a fluorinated sample was prepared using 2 M Sodium Trifluoroacetate which was dissolved in D_2O . The fourth sample was also based on a fluorinated compound using a mixture of 75 % Hexafluorobenzene and 25 % CDCl_3 . Plugs of Fluorinert FC-770 oil separated the sample plugs of the ^1H detector sample lines, to avoid susceptibility shifts due to air bubbles within the active volume of the detectors. Moreover, the oil plugs prevented cross contamination between the separated aqueous samples. Similarly, silicone oil was selected as sample separation fluid for the ^{19}F sample lines as an alternative to FC-770.

Scaling NMR spectrometer hardware for parallel measurement is challenging, as each channel requires a dedicated set including an RF source, an RF power amplifier (PA), a low noise amplifier (LNA), a mixer, RF filters, and a digitizer. Therefore, an HPPR unit was necessary to provide the preamplification and RF switching required to process the four separate FID signals. Hence, the probe was connected to the HPPR using four RF cables as shown in Fig. 1.a. Consequently, a specific console was also needed for further signal processing as shown in Fig. 1.c, which entailed a fundamental physical footprint and significant financial investment. This configuration was for a non-multiplexed acquisition to provide a baseline for our comparison.

To accommodate four detectors within the spectrometer bore, each was spatially shifted to identical off-center positions. Therefore, each detector required a dedicated set of local shim coils to compensate for field inhomogeneities. One challenge was optimizing the local shims and the global vendor-supplied shim set (with an origin set to the magnet axis) to achieve homogeneous field regions across each detector. A dedicated multichannel shimming current source box was used, capable of providing stable, high-precision DC currents to the four shim sets. In addition, an external matching and tuning box was used to adjust the matching and tuning capacitors for each detector. This allowed for fine-tuning of the resonance frequencies, and ensuring impedance matching for each independent detector to minimize reflective losses. By taking advantage of this configuration, we were able to perform non-multiplexed parallel NMR experiments with simultaneous four-channel acquisition. We note here the large physical footprint of the console, its cost due to the increased number of technical interfaces for RF, shims, and gradients, and the extensive RF cable bundle which introduced significant spatial crowding inside the probehead, all of which hamper the workflow of the spectroscopist.

The primary benefit of signal multiplexing extends beyond the reduction in physical cabling. It provides a fundamental shift in NMR system architecture. Upon scaling the number of detectors, multiplexing enables the consolidation of multiple FID signals into a single shared transmission line. In addition to reducing the physical footprint and eliminating inter-cable crosstalk and noise interference, it allows for a tremendous reduction in the size, cost, and complexity of the NMR system by decreasing

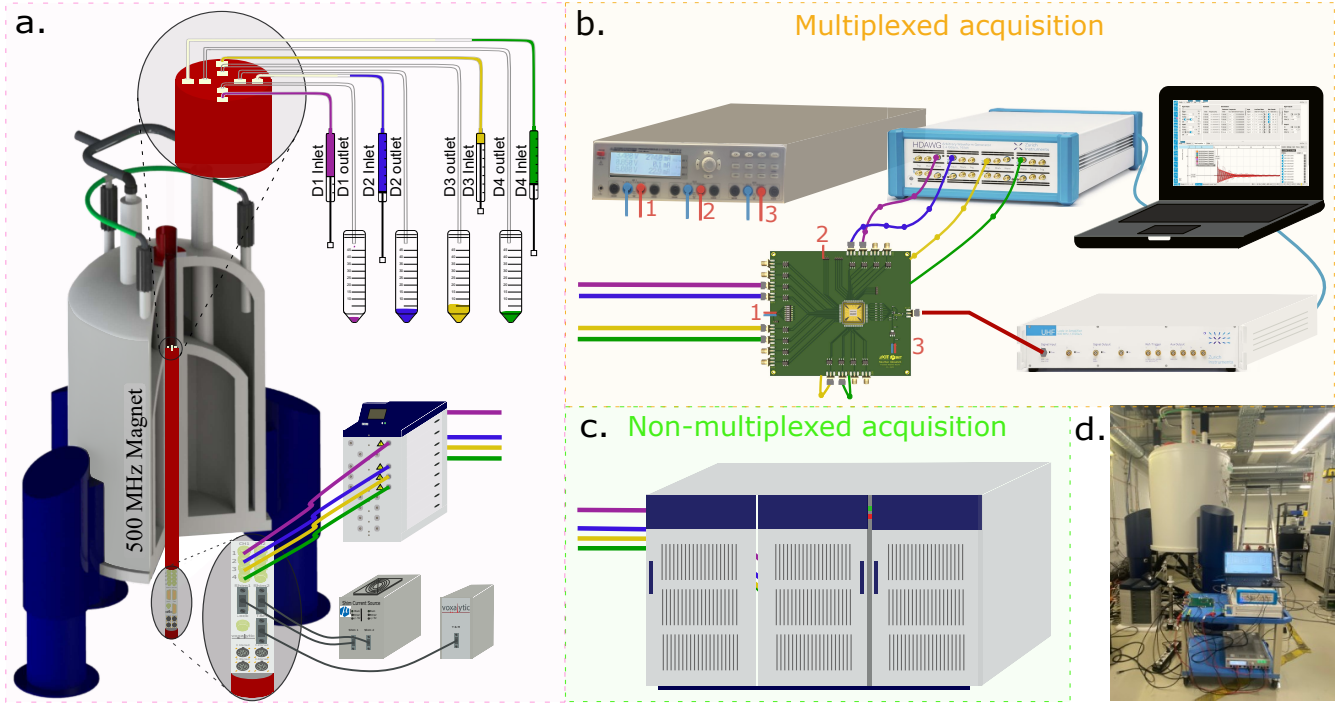


Figure 1. An overview of the main components of the reported setup for multiplexed NMR spectroscopy. a) *Reference setup*: A four-detector parallel NMR probe, mounted in an 11.74 T NMR magnet, was connected to an eight-channel preamplifier unit. An external matching and tuning box was connected to the probe. Each detector featured localized shimming through a shimming current source box. b) *Alternative setup*: Our multiplexing setup involving a customized CMOS multiplexer, mounted on a PCB and equipped with its own power supply. A 750 MHz arbitrary waveform generator (HDAWG) produced the required local oscillator signals. On the right, a 600 MHz lock-in amplifier (UHFLI) further processed the multiplexed NMR signal. A laptop controlled both the waveform generator and the lock-in amplifier. c) *Conventional NMR spectrometer*: The non-multiplexed NMR signal was directly connected via a vendor-supplied preamplifier to a multi-channel NMR console. d) *Experimental setup photograph*: Both experiments were performed using the same magnet and probe.

the required number of RF receivers from N (number of detectors) to 1 (number of RF cables). To facilitate simultaneous parallel acquisition across all channels, this system utilizes frequency division multiplexing (FDM) by modulating each detector signal $j \in \{1, \dots, N\}$ to a unique frequency carrier f_j . For our experiment we selected $N = 4$. For FDM, each FID signal was assigned to a separate frequency leaving an inter-channel spacing of 5 MHz. To do so, we employed a CMOS frequency division multiplexing chip that was previously developed in the group by Jouda et al.¹⁵. The eight-channel CMOS FDM receiver chip was demonstrated for 400 MHz phased array magnetic resonance imaging (MRI). The CMOS chip consists of eight channels, each of which has a low noise amplifier (LNA), a frequency mixer, and a band-pass filter (BPF). Hence, NMR signals are initially amplified through the LNA to enhance the signal to noise ratio and compensate for any prior attenuation. In the following, frequency mixers were implemented for down-conversion to a lower intermediate frequency (IF) based on external local oscillator signals that were generated by the 750 MHz arbitrary waveform generator (HDAWG, Zurich Instruments) as shown in Fig. 1.b and fed into the CMOS chip. Each channel was designed for a specific intermediate frequency to match the center frequency of the following BPF stage. The eight BPFs were designed with center frequencies of 10 MHz, 15 MHz, 20 MHz, 25 MHz, 30 MHz, 35 MHz, 40 MHz and 45 MHz, respectively. To prove the concept of frequency multiplexing for parallel experiments, the CMOS FDM receiver was implemented as shown in Fig. 1.b. The pre-amplifier (HPPR) signal was directly connected to the input of the CMOS chip channels 3, 4, 5 and 6, respectively, thus bypassing the MR console. Now consider each j^{th} FID signal as follows,

$$S_{\text{FID},j}(t) = m_j(t)e^{i2\pi f_{0j}t}, \quad (1)$$

where $m_j(t)$ is the base-band of the MR signal j , and f_{0j} is its Larmor frequency. Then, a mixer is utilized for frequency down conversion, for example, the first NMR signal (FID₁) had a frequency of 500 MHz, which needed to be converted down to an intermediate frequency (IF) of 20 MHz, i.e., at the center frequency of the third BPF channel of the CMOS chip. Hence, a local

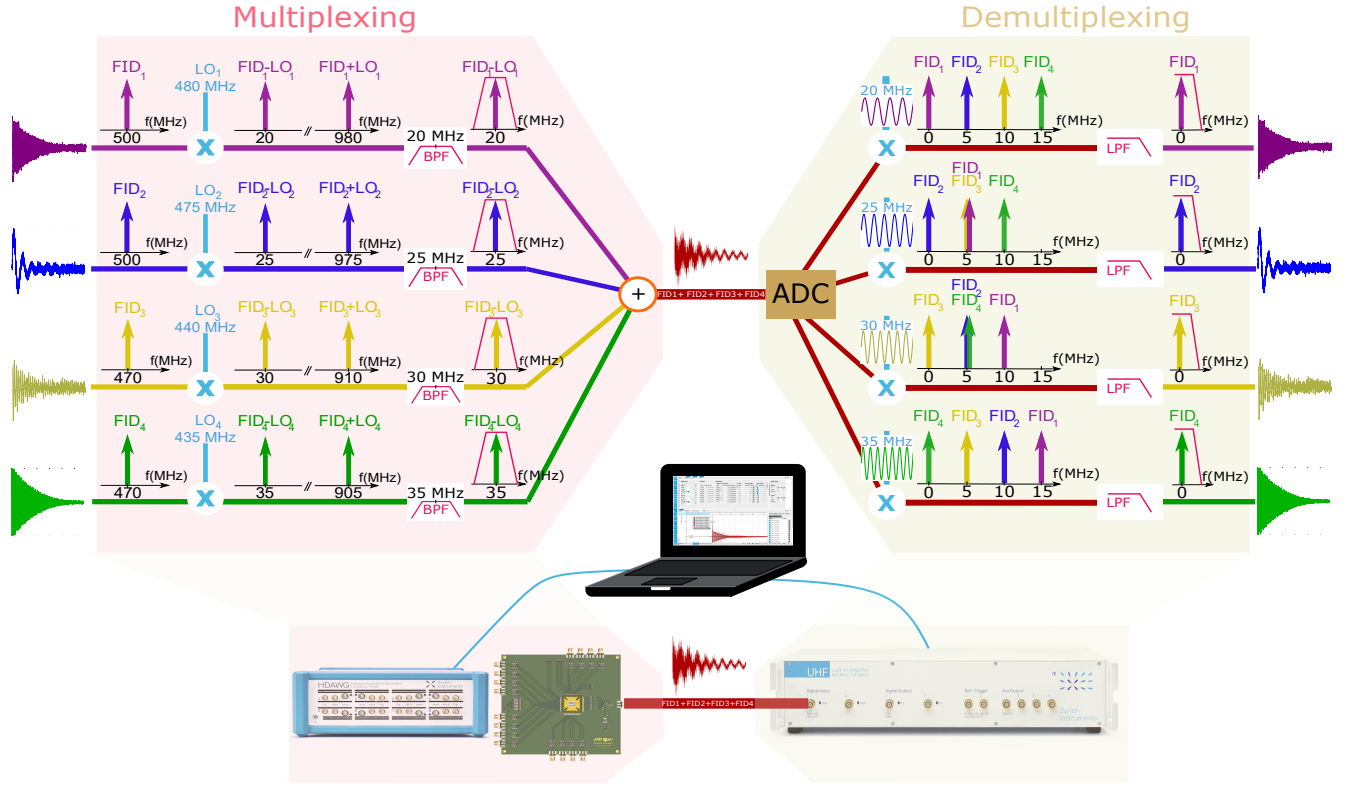


Figure 2. Multiplexing and demultiplexing scheme for four parallel NMR signals.

oscillator signal of frequency 480 MHz was required for the mixer, resulting in the output

$$S_{IF,j} = S_{FID,j}(t) \cdot LO_j(t) = m_j(t) e^{i2\pi f_{0j}t} \cdot e^{-i2\pi f_{LOj}t} = m_j(t) e^{i2\pi(f_{0j} - f_{LOj})t}. \quad (2)$$

Similarly, to convert down FID₂, FID₃ and FID₄, local oscillator signals of 475 MHz, 440 MHz and 435 MHz were needed. Then, band-pass filters were used to suppress all high-frequency sideband signals. Fig. 2 shows in detail the signal processing blocks of the four FID signals through the multiplexing stage. At the end of multiplexing, signals were superimposed using a high-speed operational amplifier LMH6629 (Analog Devices, Wilmington) without interference, as long as each signal possessed a unique frequency band. Consequently, a shared cable was deployed to deliver the signals for post processing. Each channel of the CMOS chip required around 54 mA from a 3.3 V source¹⁵, or a total of 0.756 W for the four channels, the signal sources excluded.

One shared cable was connected between the output of the multiplexer PCB and the input channel of the 600 MHz lock-in amplifier (UHFLI, Zurich Instruments) used for post-processing. The demodulators of the UHFLI were essential for demultiplexing the NMR signals for further individual signal processing. The UHFLI had digital demodulators, and although they were more complex than analog demodulators, because they performed additional processing such as synchronization and error correction to recover digital bits accurately from the received signal, they were more robust against noise and interference. As shown in Fig. 2, the first stage of the demultiplexing stage was the 1.8 Gs⁻¹ analog to digital converter. The UHFLI had eight demodulators with eight internally implemented oscillators. Four demodulators and oscillators were used to demultiplex the four NMR signals. The frequency of the first four oscillators were adjusted to 20, 25, 30 and 35 MHz, respectively. The frequency mixers of the demodulators converted the frequency of each NMR signal down to the base-band frequency. Accordingly, the four NMR signals were recovered from the signal streams by using 20 kHz low pass filters (LPF).

Experiment (2): System Design

Fig. 3 shows the setup of the second experiment. The main difference with respect to the first experiment was replacing the Voxalytic multi-detector probe with a Bruker broadband probe. This single-sample probe utilized two NMR coils. The inner coil was optimized for carbon ¹³C, and the outer coil for proton ¹H. Each channel had an independent RF port. The experiment was deployed in a Bruker 9.4 T (400.2 MHz larmor frequency for proton) NMR spectrometer. The sample consisted of 0.1 M ¹⁵N-labeled urea and 0.1 M ¹³C methanol (CH₃OH) dissolved in DMSO-d₆. This corresponded to standard samples normally

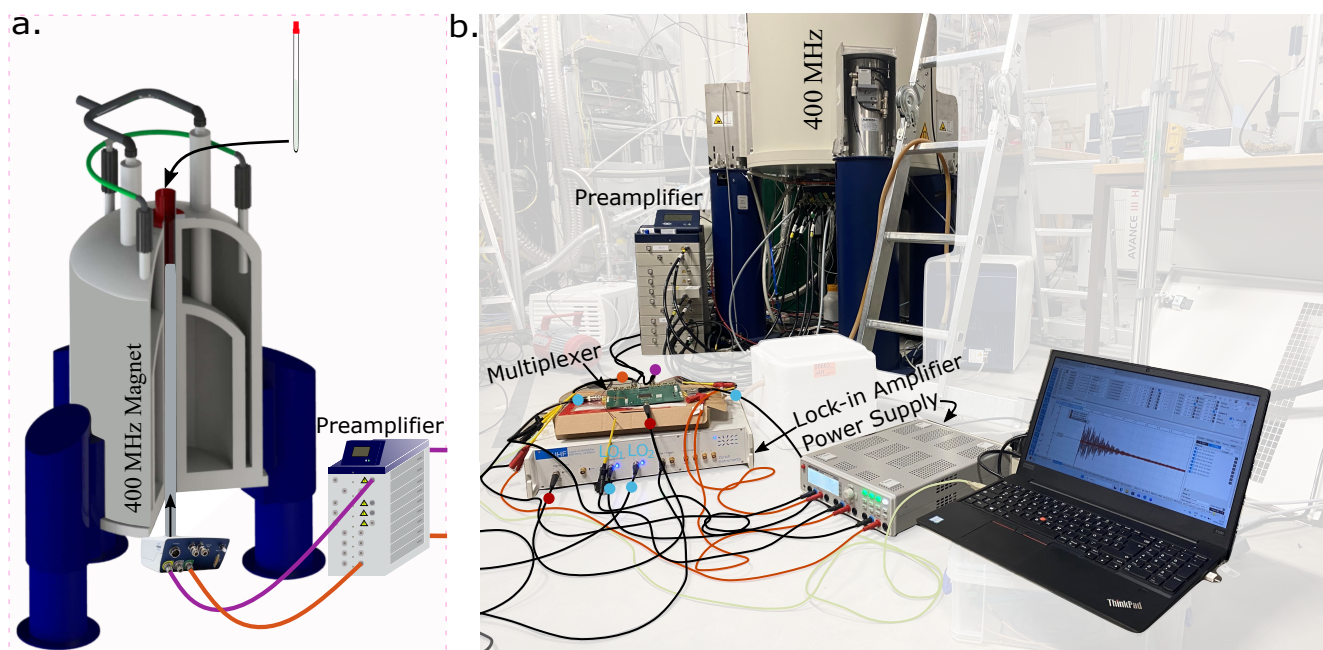


Figure 3. Setup for the multi-nucleus experiment a) A broadband probe is mounted on a 9.4 T NMR magnet and connected to an eight-channel preamplifier unit. b) Laboratory setup of the experiment with all required units for multiplexed acquisition.

provided by Bruker. For non-multiplexed acquisition, the preamplifier was connected directly to a console similar to experiment (1) as shown in Fig. 1.c, and the RF port of the ^1H was connected to the first port of the preamplifier and the RF port of ^{13}C was connected to the eighth port of the preamplifier. For multiplexed acquisition, two NMR signals were considered, with the ^1H port of the preamplifier connected to channel 4 of the multiplexer PCB corresponding to a 25 MHz center frequency BPF. Additionally, the ^{13}C port was connected to channel 5 corresponding to 30 MHz. The two local oscillator signals were provided by the lock-in amplifier, which had two output ports. Therefore, the HDAWG waveform generator was not required for this experiment. The first local oscillator (^1H) was set to a frequency of 375 MHz to achieve a 25 MHz intermediate frequency. Similarly, the second local oscillator (^{13}C) was adjusted to 70 MHz to yield a 30 MHz intermediate frequency.

Results

Experiment (1): Experimental Verification of a Four-Channel Multiplexed NMR System

Following sample loading, each detector was independently tuned and matched. A combination of global and localized shimming was then optimized using the dedicated shimming current source box to ensure field homogeneity for each detector. Initial measurements were performed in a non-multiplexed acquisition to establish a baseline reference. Four simultaneous 90° pulses were applied to excite the samples independently across the four channels. Fig. 4.a shows the ^1H spectra obtained via non-multiplexed acquisition. Fig. 4.b illustrates the results for ^{19}F spectra.

For accurate measurements based on the observed set frequency of each detector 500.137, 500.137, 470.567 and 470.517 MHz, the HDAWG oscillators were set to 480.137, 475.137, 440.467 and 435.517 MHz, respectively, to maintain the target intermediate frequencies. Consequently, the UHFLI oscillators were adjusted to 20 MHz, 25 MHz, 30 MHz and 35 MHz. The CMOS chip consumed 283.5 mA from a 3.4 V source for the four channels, in addition to 0.1 mA from a 0.85 V source for bias adjustment. Additionally, 22.8 mA was consumed from a 6 V source for the operational amplifier LMH6629. This amounted to 1.1 W of peak power consumption to consolidate the digital signals into a single data stream. A positive edge trigger with a threshold of 100 mV was configured on the UHFLI to initiate the capture of the multiplexed signal and start demultiplexing it. The data transfer rate of each demultiplexed signal from the UHFLI to laptop was adjusted to 219.7 kSPS.

Fig. 4.c and 4.d show the ^1H and ^{19}F spectra obtained via multiplexed acquisition. By comparing the multiplexed and non-multiplexed spectra, it revealed that peak positions and intensities were well-preserved, validating the signal integrity of the multiplexing scheme. The visibility of weak signals could be enhanced by adjusting the amplitude of the local oscillator signal in the HDAWG. Fig. 4.d and 4.e illustrate the enhancement of the detector 3 peak after doubling the oscillator signal amplitude of the fifth channel of the CMOS chip. A further potential improvement during post-processing involved signal decoupling to suppress crosstalk between detectors as shown in Fig. 4.f, hence enhancing signal isolation. Fig. 4.g displays the

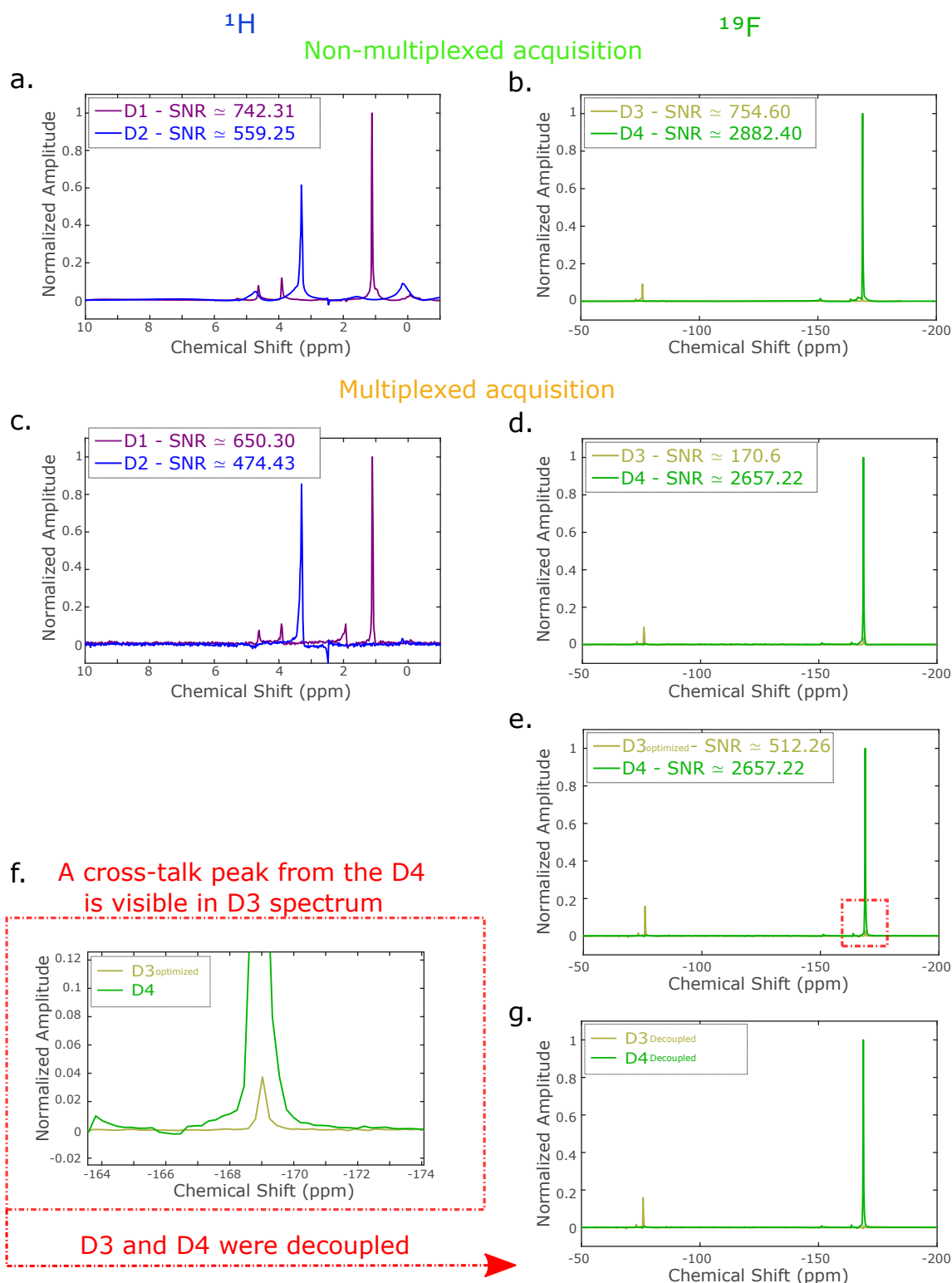


Figure 4. Non-Multiplexed and Multiplexed NMR signal acquisition and processing. a) Non-multiplexed ^1H NMR spectra of detectors 1 and 2. b) Non-multiplexed ^{19}F NMR spectra of detectors 3 and 4. c) Multiplexed NMR spectra of detectors 1 and 2. d) Multiplexed NMR spectra of detectors 3 and 4. e) The NMR spectrum of detector 3 is optimized by increasing the amplitude of the local oscillator signal LO_3 . f) cross talk between detector 3 and 4 was observed. g) Crosstalk was suppressed through post processing.

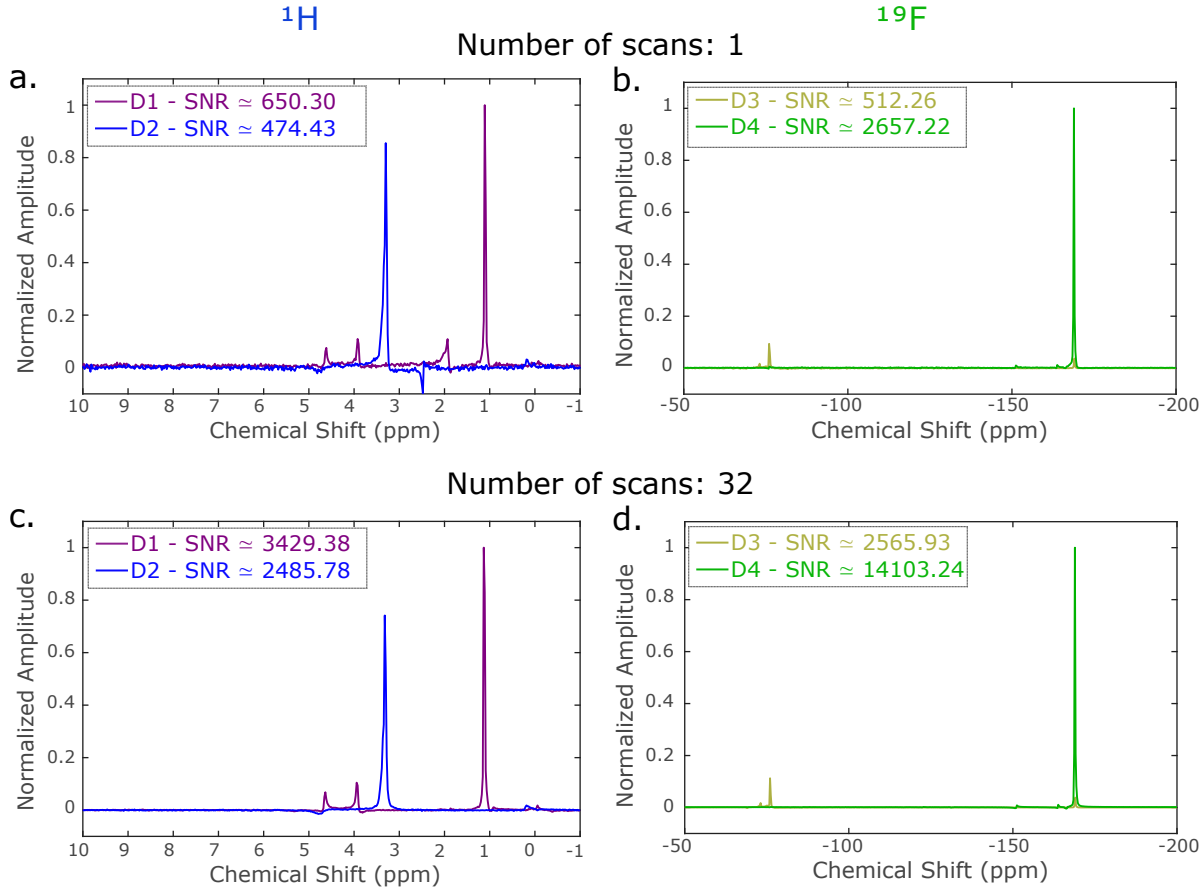


Figure 5. Signal to Noise ratio enhancement with increasing number of scans. a) Single scan proton ^1H spectra. b) Single scan fluorine ^{19}F spectra. c) Averaged proton ^1H spectra for 32 scans. d) Averaged fluorine ^{19}F spectra for 32 scans.

^{19}F spectrum after applying a digital decoupling algorithm in MATLAB, which successfully achieved crosstalk cancellation. This involved a MATLAB-based algorithm that performed a weighted subtraction, using a weighting factor of 3.5 %, to remove the interference signal of detector 4 from the target signal of detector 3.

After the multiplexing scheme was implemented, a degradation of the linear amplitude SNR was observed. As detailed in Table 1, detector 4 exhibited the lowest value with 7.81 % degradation, while detector 3 experienced the highest at 32.12 %. To improve the signal-to-noise ratio (SNR), signal averaging was considered by increasing the number of scans from 1 to 32. This yielded an enhancement factor of $\sqrt{32} \approx 5.66$. For synchronized data acquisition, the positive edge trigger count on the UHFLI was scaled to match the number of scans, ensuring that all multiplexed signals were captured. The resulting spectra, as shown in Fig. 5, demonstrate the SNR enhancement achieved through accumulation. For example, for detector 1, the SNR improved from approximately 650.30 to 3429.38 as observed in Fig. 5a and 5c. The experimental gain of 5.27 closely matches the theoretical predictions. Similarly, Fig. 5b and 5d compare the enhancement for ^{19}F spectra. The proximity of enhancement factors from Table 1 to the theoretical limit confirmed the chip's performance stability and that the noise floor remains uncorrelated across successive scans.

Detector #	Non-multiplexed SNR	Multiplexed SNR	Degradation %	Averaging SNR	SNR enhancement factor
1	742.31	650.30	12.39	3429.38	5.27
2	559.25	474.43	15.17	2485.78	5.24
3	754.60	512.26	32.12	2565.93	5.01
4	2882.40	2657.22	7.81	14103.24	5.31

Table 1. SNR performance of four detectors for non-multiplexed, multiplexed, and 32-scan averaging acquisitions

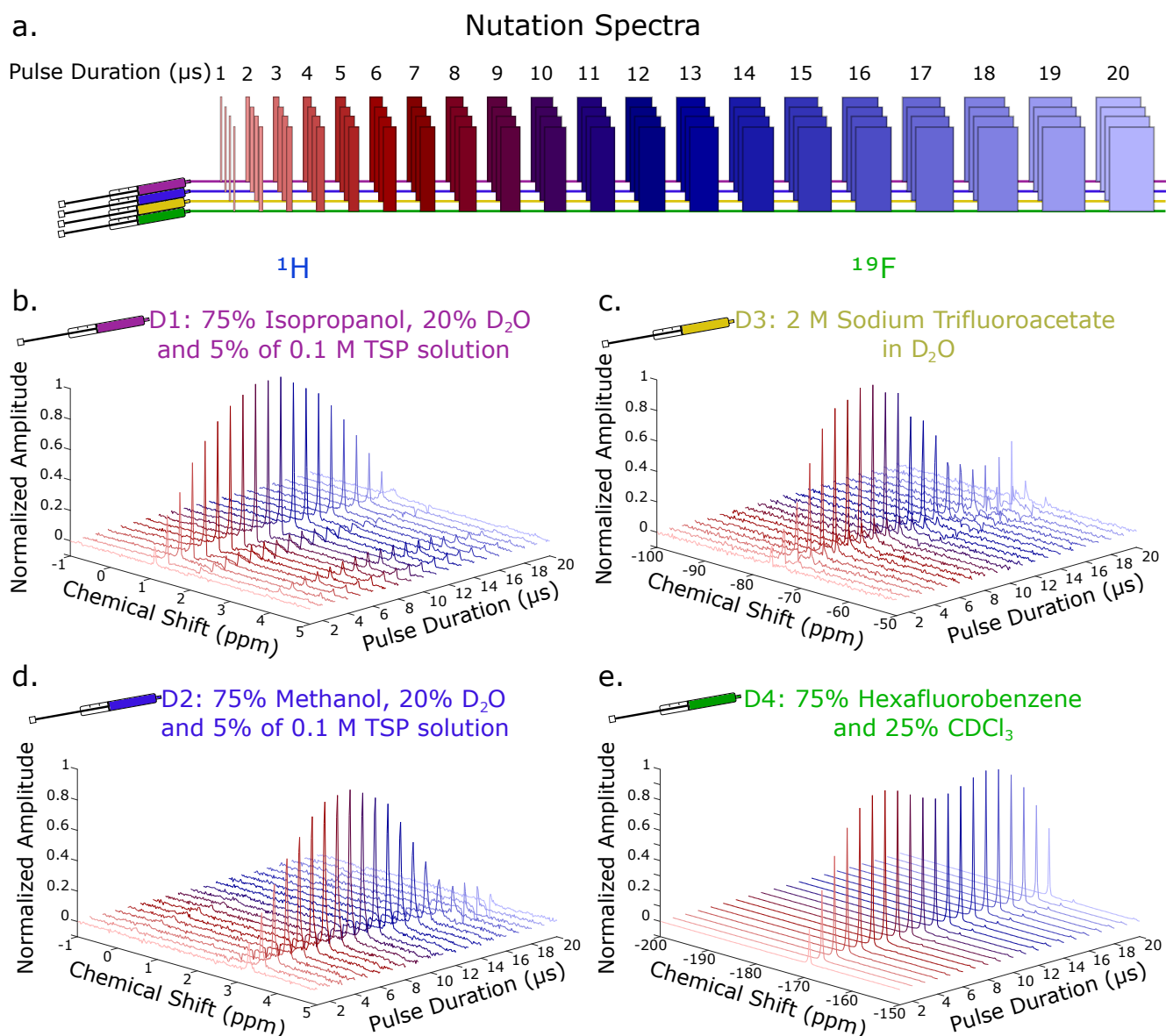


Figure 6. Multiplexed parallel nutation spectra for four distinct samples. a) Experimental timing sequence overview. b) Sample: 75% Isopropanol, 20% D_2O and 5% of 0.1 M TSP solution. c) Sample: 2 M Sodium Trifluoroacetate in D_2O . d) Sample: 75% Methanol, 20% D_2O and 5% of 0.1 M TSP solution. e) Sample: 75% Hexafluorobenzene and 25% CDCl_3 .

For high-throughput multi-detector experiments, parallel nutation measurements are essential to achieve time gain proportional to the number of detectors. In this work, rather than performing four discrete serial measurements, a single parallel nutation spectrum was acquired, reducing the total experimental time by a factor of four. Pulse-width-dependent nutation was measured by incrementing the RF pulse duration, while maintaining constant transmit power. Hence, nutation measurements were performed in parallel by sweeping the pulse duration from 1 μs to 20 μs in 20 discrete steps. A relaxation delay of 10 s was implemented between each incremental step to ensure sufficient longitudinal relaxation between pulses. Using a single scan per increment, the total acquisition for the four detectors took 3 min and 20 s. The positive edge trigger count on the UHFLI was adjusted to 20 for synchronized acquisition similar to the previous averaging experiment. Fig. 6 illustrates the nutation spectra of the four detectors. For proton spectra as shown in Fig. 6.b and 6.d, the nutation spectra demonstrate the linear scaling of the flip angle with pulse duration, resulting in the characteristic sinusoidal modulation of the signal amplitude. The pulse duration corresponding to a 90° flip angle was identified by the primary peak of the sinusoidal modulation, representing the point of maximum transverse magnetization of 9 μs from Fig. 6.b. Similar for detector 3, the corresponding pulse duration was 8 μs , as shown in Fig. 6.c. The acquired nutation spectrum in Fig. 6.e followed the expected sinusoidal trend, though a slight damping

of the modulation envelope was observed. This deviation from the ideal nutation model is attributed to B_1 field inhomogeneity across the detector volume, which prevented a perfect signal null at the 180° flip angle. Despite this damping, the 90° pulse duration remained clearly identifiable at the peak of the envelope of $7\ \mu\text{s}$ pulse duration.

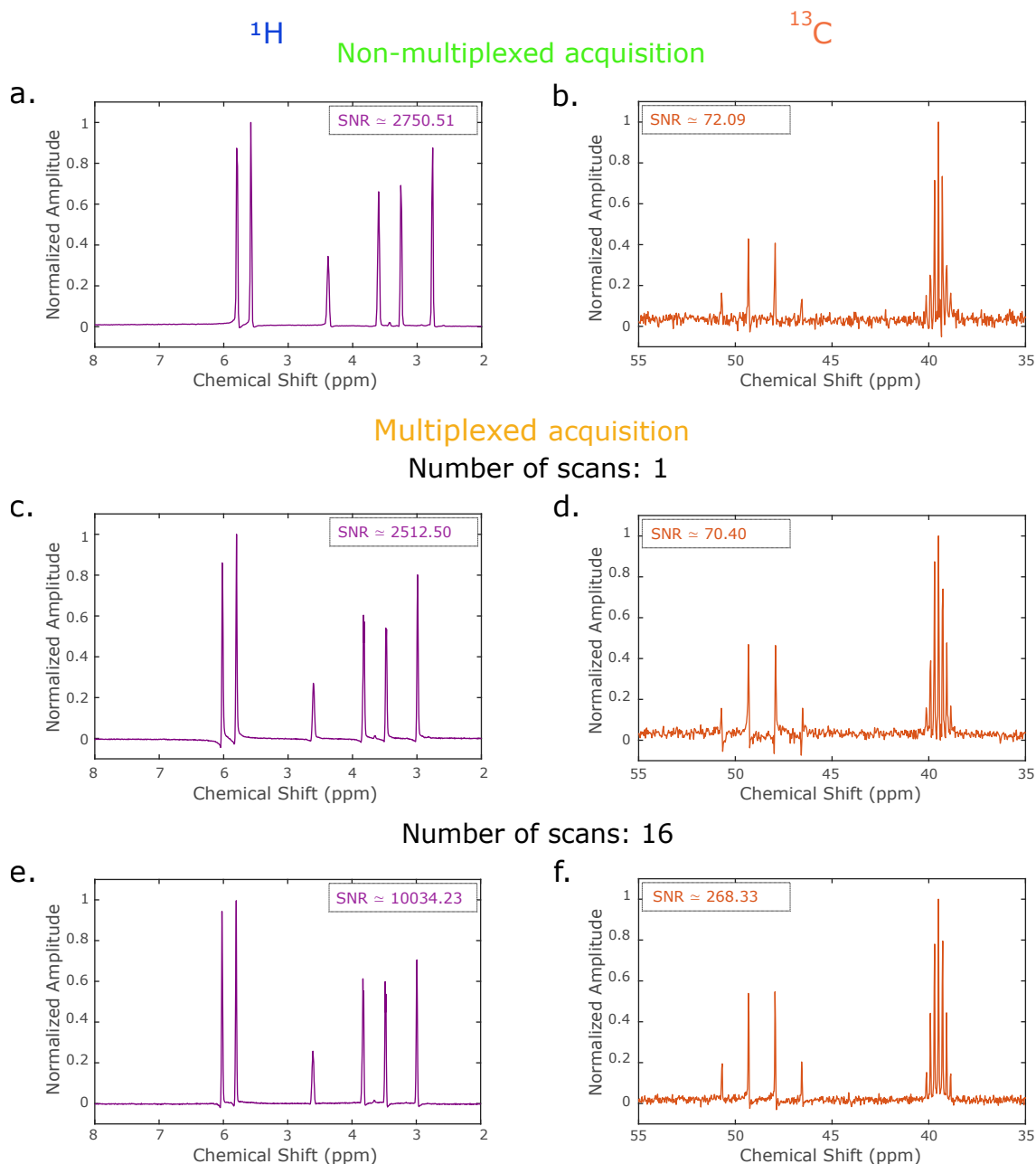


Figure 7. Multi-nucleus non-multiplexed and multiplexed acquisitions. a) Non-multiplexed proton ^1H NMR spectrum. b) Non-multiplexed carbon ^{13}C NMR spectrum. c) Multiplexed ^1H NMR spectrum acquired in parallel. d) Multiplexed ^{13}C NMR spectrum acquired in parallel. e, f) Resulting ^1H and ^{13}C NMR spectra after signal averaging of 16 multiplexed scans, demonstrating improved signal-to-noise ratio (SNR).

Experiment (2): Experimental Verification of a Multi-Nucleus Multiplexed NMR System

During experimental preparation, the four oscillators on the UHFLI (Zurich Instruments) were configured to 25, 30, 375.352 and 70.678 MHz. The first two oscillators were dedicated to the digital demultiplexing sequence. The remaining two oscillators provided the frequencies required for downconversion. These were tuned to 375.352 MHz and 70.678 MHz to mix with

the target detector frequencies of 400.352 MHz (^1H) and 100.678 MHz (^{13}C), respectively. This configuration maintained consistent intermediate frequencies of 25 MHz and 30 MHz, ensuring optimal signal processing across the parallel acquisition channels. For the two active channels, the CMOS chip consumed 125.4 mA from 3.4 V. The same trigger configuration and data rate were used in the UHFLI.

To evaluate the efficiency of multiplexed acquisition, 30° flip angle excitation pulses were implemented instead of the standard 90° . With this choice, steady-state magnetization can be maximized over multiple scans, following the Ernst angle principles¹⁶. Hence, a 16-scan averaging experiment was performed by avoiding full saturation of the ^{13}C spins, which require characteristically long longitudinal relaxation times. A 25 s delay was considered as relaxation time for the single scan parallel measurement. Fig. 7a-d illustrate ^1H and ^{13}C spectra in the case of non-multiplexed and multiplexed acquisitions. The ^1H channel produced high-quality spectra, whereas the ^{13}C signal exhibited a lower SNR. This difference was attributed to the lower gyromagnetic ratio (γ) of 10.70 MHz T^{-1} , and the natural abundance of 1.1 % of ^{13}C , which reduces its receptivity. Consequently, the carbon channel required signal averaging to lift the signal above the thermal noise floor. Signal averaging of 16 scans significantly enhanced the ^1H spectral quality, the improvement in the ^{13}C channel was less pronounced. The $\sqrt{N}$ SNR improvement of 16 scans was insufficient to yield a high-contrast spectrum compared to the more receptive ^1H nuclei with gyromagnetic ratio of 42.57 MHz T^{-1} and natural abundance 99.98 % as observed in Fig. 7e and 7f.

This experimental scenario was intentionally pursued to test the robustness of our multiplexed framework and the efficacy of our post-processing routines. Through the application of optimized window functions and digital filtering in MATLAB, the multiplexed acquisition achieved a better SNR compared to the non-multiplexed reference for single-scan data of ^{13}C . This suggests that the multiplexed framework, when combined with tailored post-processing algorithms, can mitigate some of the sensitivity losses typically associated with multi-channel parallel detection. The raw FIDs were first corrected for DC offset and truncated to remove initial acquisition artifacts and group delay. Sensitivity enhancement was achieved by applying an exponential window function, $e^{-\pi LBt}$, with a line-broadening factor (LB) of 1 Hz. This targeted apodization effectively suppressed late-stage noise, yielding the enhancement in SNR for the single-scan multiplexed spectra.

A minor linear amplitude SNR degradation was detected when comparing the the non-multiplexed and multiplexed signals. The ^1H channel exhibited an 8.65 % degradation, whereas the ^{13}C channel exhibited a negligible degradation of 2.34 %. The difference of degradation could be the result of the differing Larmor frequencies of isotopes, because the ^1H channel operates at a significantly higher Larmor frequency than ^{13}C , so the system is more sensitive to impedance mismatches and parasitic capacitances of the multiplexing hardware. Moreover, the proximity and shielding of the coils could impact the SNR degradation. Then, a 16-scan averaging configuration was applied. A theoretical SNR enhancement of a factor of 4 could be achieved. The system achieved SNR enhancement factors of 3.99 for ^1H and 3.88 for ^{13}C . Approaching the theoretical values proved phase and amplitude stability of the multiplexing system over time.

Discussion

Our main objective was to establish that four independent NMR signals from four distinct detectors could be multiplexed into a single NMR acquisition channel. The comparison between the multiplexed and non-multiplexed results shows that the spectral features (chemical shifts and line shapes) of the multiplexed signals remained identical to the original signals. This shows that the heterodyne mixing and subsequent digital demultiplexing process preserves the linear characteristics of the NMR signal. A significant advantage of this multiplexed framework is the ability to apply digital decoupling during postprocessing. A primary challenge in multi-detector arrays is the electromagnetic coupling between adjacent coils, which can result in signal leakage or crosstalk. To address this, we implemented a digital decoupling algorithm in MATLAB that successfully achieved crosstalk cancellation between the detector channels. A MATLAB-based algorithm performed a weighted subtraction in the frequency domain, so that we e.g. were able to subtract the interfering components of Detector 4 from the target signal of Detector 3. This precise digital compensation eliminated the residual crosstalk without degrading the primary signal's integrity, demonstrating that software-based calibration can effectively mitigate the physical proximity limitations of high-density detector arrays.

The efficiency of the system is best demonstrated through the signal averaging process. In a traditional serial configuration, performing 32 scans for four separate samples would require a total of 128 separate relaxation delays. In contrast, our multiplexed setup achieved the SNR enhancement for all four samples simultaneously within only 32 total scan cycles. This parallelization of the relaxation delay represents a 400 % increase in instrument efficiency, effectively reducing the total experimental time by a factor of four and establishing this as a viable strategy for high-throughput screening. Finally, the parallel nutation measurements served as a rigorous validation of the B_1 field across the array. The ability to sweep pulse durations from 1 μs to 20 μs simultaneously for all detectors allowed for a rapid mapping of the excitation efficiency. The consistent sinusoidal modulation across all channels confirms that the multiplexing electronics did not introduce phase instability or non-linear power fluctuations, even at varying pulse widths.

The second phase of the experiment extended the multiplexing framework to heteronuclear acquisition, demonstrating the system's frequency flexibility. By coordinating four independent oscillators on the UHFLI, we managed both the Local

Oscillator (LO) generation for analog mixing, and the subsequent digital demultiplexing. This established a stable heterodyne system capable of simultaneously processing signals at 400.352 MHz ^1H and 100.678 MHz ^{13}C . A strategic 30° excitation pulse was implemented for the multi-nucleus setup, deviating from the standard 90° flip angle. This was a deliberate choice to prioritize the experimental duty cycle. Given the characteristically long longitudinal relaxation times (T_1) of ^{13}C , a 90° pulse would risk magnetic saturation, requiring excessively long recovery periods. By operating at the Ernst angle for the given 25 s relaxation delay, we maximized the SNR per unit time. This approach ensured that the ^{13}C spins remained "fresh" for subsequent scans during the 16-scan averaging process, which is critical for nuclei with such low receptivity.

The success of this multiplexed framework opens significant opportunities for scaling the number of detectors within a single NMR probe. Future designs can address the inherent challenges of physical space and inductive coupling by leveraging the high integration density of CMOS technology. The current CMOS chip architecture provides the capability to multiplex up to eight independent NMR signals. Furthermore, multiple chips can be cascaded to accommodate an even higher number of parallel channels, vastly increasing throughput. The main advantage of the compact footprint of the ASIC chip (size $\approx 3\text{ mm} \times 4\text{ mm}$) is its integration into spatially restricted NMR probe heads, reducing cable lengths and associated parasitic effects. This high level of integration supports the practical realization of multiplexed transceiver circuitry within advanced NMR hardware platforms. Looking ahead, the presented architecture provides a pathway for implementation in advanced semiconductor technologies. Although the current design is realized using a 350 nm RF CMOS fabrication process, using other technologies such as TSMC 180 nm RF CMOS or IHP SG13G2 130 nm SiGe BiCMOS technology could further increase integration density with a reduction of the die area due to the smaller feature sizes. This scaling could enable compact implementations and provide more design flexibility for NMR transceiver systems with highly integrated multiple channels.

Beyond simple signal routing, the CMOS platform allows for the integration of detection circuitry directly within the probe environment. Positioning the chip in close proximity to the micro-coils would minimize signal attenuation and resistive losses typically associated with long coaxial wiring. This integrated approach could potentially eliminate the need for external preamplifiers, especially if the design was evolved to include on-chip low-noise amplifiers (LNAs) and local oscillators. Such a "System-on-Chip" (SoC) design would provide a compact, robust, and highly scalable solution for the next generation of high-density, multi-nucleus NMR spectrometers.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author or can be downloaded from the KITopen repository.

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Author contributions statement

N.A. performed most of the preparation and experiments with support of M.J., D.B., J.L., and M.H. setting up the first experiment. D.Z. supported setting up the second experiment. N.A. and J.L. processed the data. J.G.K. and M.J. provided project supervision. N.A. drafted the initial manuscript. All authors reviewed the manuscript.

Additional information

The corresponding author is responsible for submitting a [competing interests statement](#) on behalf of all authors of the paper. This statement must be included in the submitted article file.