Next-generation Multidimensional NMR Spectrometer Based on Semiconductor Technology

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We recently integrated all major functions – RF transmitter, RF receiver, and arbitrary pulse sequencer – of the conventionally bulky NMR spectrometer electronics into a fingertip-sized silicon chip and demonstrated various multidimensional NMR spectroscopy experiments with them, using various bio- and organic molecules. We envision that the size and cost economy of such integrated spectrometer chips can open up new exciting vistas in the science and technology of NMR. For example, high-throughput structural analysis of macromolecules can be enabled by operating a large number of the spectrometer chips in parallel inside a high-field superconducting magnet. For another example, online, on-site small-molecule analysis can be performed in a miniaturized, thus portable, platform that combines a spectrometer chip with a low-field compact permanent magnet. In this article, we will discuss the technical background and outlook of this recent synergy between semiconductor chip technology and NMR science.

Keywords: NMR spectroscopy, multidimensional NMR spectroscopy, semiconductor, semiconductor chips, integrated circuits

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Fusing NMR Science with Semiconductor Technology

Silicon integrated circuits, fabricated with what is called complementary metal-oxide semiconductor (CMOS) process, represent an enormously fruitful technological paradigm that has made possible today's computers and communication devices. The tremendous usefulness of the silicon integrated circuits originates from their integration of complex electronic functions into a tiny footprint at low cost. Think of the magic of the computer chip that contains billions of transistors in the area of just a few hundred square millimeter and computes hundreds of gigabytes of data per second!

It is then possible to imagine integrating the conventionally bulky NMR spectrometer electronics into a silicon chip to capitalize its cost and size economy. Historically, though, the NMR science has remained largely orthogonal to the semiconductor chip technology. It is only in the more recent years that NMR electronics started being integrated into silicon chips (Figure 1). Specifically, in 2008–2011, we reported a series of silicon NMR electronics chips that can excite nuclear spins and subsequently measure their relaxation times[1–5] with an integrated Carr–Purcell–Meiboom–Gill (CPMG) pulse sequencer (Figure 1a–c). Other scientists developed silicon chips that can acquire one-dimensional (1-D) NMR spectra (as opposed to relaxometry) with the help of external pulse sequencers.[6–8] In 2014, building upon these prior works, we reported for the first time the integration of all essential functions of modern multidimensional NMR spectrometers—RF transmitter, RF receiver, and arbitrary pulse sequencer—into a silicon chip[9] (Figure 1d). These latest silicon chips performed a broad variety of two-dimensional (2-D) NMR spectroscopies such as COSY, *J*-resolved spectroscopy, heteronuclear single quantum coherence spectroscopy (HSQC), and heteronuclear multiple quantum coherence spectroscopy (HMQC), as well as 1-D spectroscopy and CPMG relaxometry, with biomolecules such as metabolites and amino acids, small-molecule drug compounds, petrochemicals, and other organic molecules. This development[9] represents a decisive step toward crystallizing the marriage of semiconductor technology and NMR science.

With their cost/size economy, such spectrometer chips will have a profound impact in the science of NMR. We envision three particular benefits. First, the spectrometer chip is small enough to be placed proximate to the sample coil inside a magnet, doing away with the signal loss encountered in the traditional setup with a long RF cable between the spectrometer electronics outside a magnet and the sample coil inside the magnet. To appreciate the feasibility of this proximate placement, consider the spectrometer chip (Figure 1d) from the latest work of ours,[9] which occupies an area of only 4 mm^2 with a thickness of 0.75 mm; this chip volume of only 3 μl is over 100× smaller than the typical sample volume in a standard 5 mm NMR tube (300–600 μl). This is dramatically opposite to conventional NMR technology, where the spectrometer electronics is far larger than the sample. Such a small spectrometer chip could be placed next to the coil inside the magnet. Even heteronuclear NMR configurations could be realized by placing

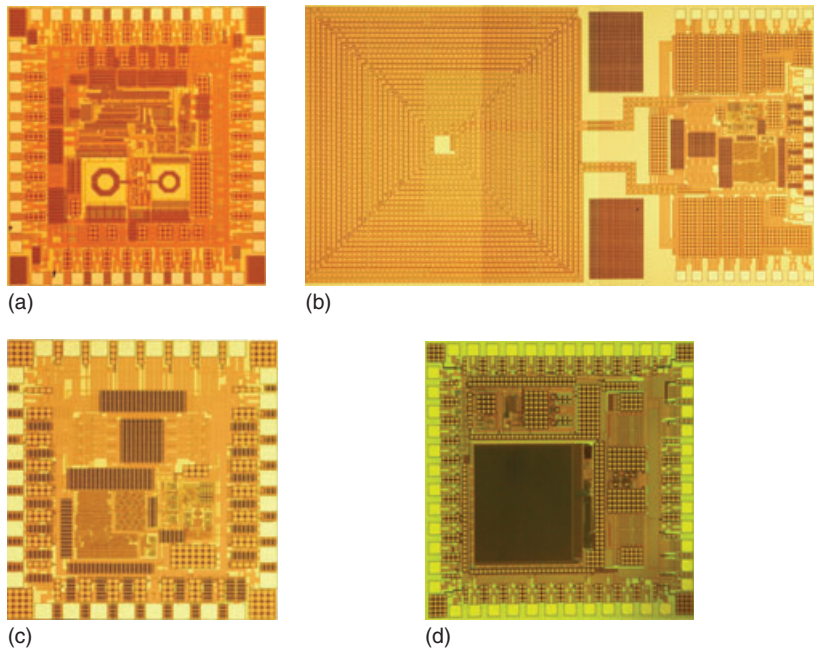

Figure 1. Silicon NMR electronics chips from our research group. (a–c) Three CPMG relaxometer chips. (d) The first spectrometer chip capable of multidimensional NMR spectroscopy. (Parts A–C © 2008, 2009, 2010, 2011 IEEE. Reprinted, with permission from Y. Liu, N. Sun, H. Lee, R. Weissleder, and D. Ham, ISSCC Dig. Tech. Papers, 2008, 140., N. Sun, Y. Liu, H. Lee, R. Weissleder, and D. Ham, IEEE J. Solid-State Circ., 2009, 44, 1629., N. Sun, T.-J. Yoon, H. Lee, W. Andress, V. Demas, P. Prado, R. Weissleder, and D. Ham, ISSCC Dig. Tech. Papers, 2010, 488, and N. Sun, T.-J. Yoon, H. Lee, W. Andress, R. Weissleder, and D. Ham, IEEE J. Solid-State Circ., 2011, 46, 342. Part D modified from D. Ha, J. Paulsen, N. Sun, Y.-Q. Song, and D. Ham, Proc. Natl. Acad. Sci. U.S.A., 2014, 111, 11955)

a few chips (each tuned at its own NMR frequency) proximate to the sample coil.

Second, many NMR applications in chemistry and biotechnology involve small molecules, for which a portable, affordable, and low-maintenance permanent magnet in lieu of a large, expensive, and high-maintenance superconducting magnet may be used.[10,11] In fact, scientists have developed compact permanent magnets whose field homogeneity is good enough for small-molecule NMR spectroscopy.[10,12,13] The spectrometer chips then can complement this advance in magnet miniaturization, enabling the *overall* system miniaturization, as we reported in 2014[9] (Figure 2; the permanent magnet is a 0.51 T NdFeB Halbach magnet). Such an overall portable NMR spectroscopy system may facilitate on-demand, online analysis of small molecules in the context of quality control, chemical reaction monitoring,[14] and metabolic fingerprinting (as opposed to more complex metabolic profiling). The overall system miniaturization can also facilitate co-use of small-molecule NMR spectroscopy with other analytical tools such as liquid chromatography and capillary electrophoresis.[15,16]

Third, for applications in structural biology and pharmaceutical screening where a high-field superconducting magnet is critical for the elucidation of the 3-D structure, conformational change, and interaction of biological macromolecules such as proteins, we envision that by arranging a large number of the spectrometer chips with their respective analytes/coils inside the superconducting magnet and by operating them independently and simultaneously, massively parallel spectroscopy can be performed. Such parallelization is possible to imagine, owing to the small size and low cost of the spectrometer chips; it would be daunting to realize with conventional bulky spectrometer electronics. If successful, the parallelization would counter the inherent slowness of NMR spectroscopy, achieving a high-throughput paradigm that may prove to be a strong value to structural biology and drug discovery where the workload is ever increasing.

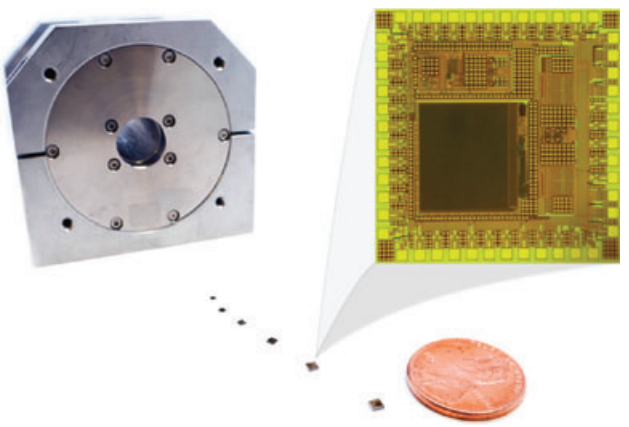

Figure 2. Portable NMR spectroscopy system that combines a 0.51 T NdFeB permanent Halbach magnet with the silicon spectrometer chip of Figure 1(d). (Modified from D. Ha, J. Paulsen, N. Sun, Y.-Q. Song, and D. Ham, Proc. Natl. Acad. Sci. U.S.A., 2014, 111, 11955)

Integration of the NMR Spectrometer Electronics

The spectrometer electronics capable of multidimensional NMR spectroscopy consists of three major building blocks: RF receiver, RF transmitter, and arbitrary pulse sequencer. All these three major functionalities can be integrated into a single silicon chip, as we recently demonstrated for the first time[9] (Figure 1d). As this chip is the only one that can perform multidimensional NMR spectroscopy with the integrated capability to generate an arbitrary RF pulse sequence among the integrated NMR electronics chips reported so far,[2−8] we will use it as a primary demonstrational vehicle in discussing the various aspects of the spectrometer electronics integration, although we will also discuss other examples. Figure 3 illustrates the schematic of this chip with some circuit details. In terms of the overall architecture, our spectrometer chip is not too different from that for the bulky conventional spectrometer electronics implemented at the discrete level. However, the key point lies in how to implement the NMR spectrometer architecture into the silicon chip by properly designing various circuit blocks and their connections so that the integrated chip can still perform suitably for multidimensional NMR spectroscopy experiments.

Before going into the details, note that an NMR spectrometer chip could integrate multiple NMR excitation/monitoring channels for different NMR-active nuclei, such as the prevalent ^{1}H and isotopes such as ^{13}C and ^{15}N. Alternatively, a single chip can integrate only a single NMR channel as in Ref. 9 (Figure 1d), and a few of such modularized chips can be put together for heteronuclear NMR spectroscopy (in the massively parallel NMR spectroscopy mentioned in the previous section, such set of a few chips representing different NMR-active nuclei channels would be altogether parallelized). While both scenarios are equally feasible, our discussion will be based on the latter scenario for simplicity, as there is no fundamental difference between them in terms of integration or experimentation challenges.

RF Receiver

The RF receiver (Figure 3, bottom) amplifies the RF voltage signal across the coil induced by nuclear spin precessions, and subsequently frequency-down converts the amplified RF signal into phase-sensitive audio-frequency signals. The former is done by the front-end low-noise amplifier. The latter is performed by the mixers driven by quadrature local oscillators. The NMR spectrum is then obtained by taking the FT of the audio-frequency signals.

As the spin precession signal is inherently weak, the degradation of the signal-to-noise ratio (SNR) by the receiver noise should be minimized. A recipe toward this goal, which is well established and widely used in the conventional setup, entails two measures. The first and rather obvious measure is to minimize the receiver's input-referred noise N_r^2 (Figure 3); the receiver noise is dominated by the noise of its front-end amplifier,[2,9] thus the first step is commensurate with designing a low-noise front-end amplifier. The second measure is to add a tuning capacitor C_c in parallel with the coil so that it resonates with the coil inductor L_c at the NMR frequency (Figure 3); with this resonance, both the spin precession voltage signal squared and thermal noise $N_c^2 = 4k_BTR_c$ (where k_B is the Boltzmann constant, T the temperature, and R_c the parasitic resistance of the coil) from the source (coil) appear at the receiver input after being *passively* amplified by a gain of $\sim Q^2$, where Q is the quality factor of the coil (in principle, this is the quality factor of the L_cC_c resonator, but in practice, it is dominated by that of the coil, because the capacitor is typically not as lossy as the coil; if the capacitor is as lossy, it adds noise and thus this technique will not be effective). Overall, the second step boosts both the signal and noise from the source, while the first step minimizes the receiver noise; taken together, they minimize the SNR degradation by the receiver noise.

This two-step technique can be used with the spectrometer chip, because a low enough noise N_r^2 can be attained for the integrated silicon receiver and the coil, which works best in a discrete implementation, has a Q on the order of 10's (the shunt capacitor C_c would be also not integrated). For example, in our work[9] (Figure 3), we achieved the receiver noise of $N_r^2 = 0.82^2$ (nV)^2 Hz^{-1}, while the intrinsic source noise $N_c^2 = 0.11^2$ (nV)^2 Hz^{-1} (along with the spin precession voltage signal squared) was boosted to $Q^2N_c^2 = 3.47^2$ (nV)^2 Hz^{-1} with $Q = 31.5$ at the receiver input, which is ~18 times larger than the receiver noise, N_r^2. Therefore, the receiver noise figure – which is the ratio of the SNRs before and after the receiver (a smaller figure corresponds to a better performance) – was only 1.06 (i.e., the SNR degradation due to the receiver noise was only by ~6%). In fact, this noise figure minimization technique works more effectively with the spectrometer chip,[2,9] as such small chip can be placed proximate to the sample coil and the shunt capacitor with no appreciable insertion loss. By contrast, in the conventional setup, the coil is connected to the spectrometer electronics with a long RF coaxial cable, which introduces loss (and thus noise) and also requires care in selecting the proper shunt capacitor value due to the impedance transforming effect of the coaxial cable.[2]

Once the signal is low-noise amplified, RF mixers driven by quadrature local oscillators down convert it to audio-frequency signals (Figure 3), as signal digitization (in order to take the fast FT) is easier at audio frequencies. The integration of the RF mixers in a silicon chip with a linearity range sufficient for NMR signals has been demonstrated by us as well as other authors.[1−4,9] Integrating the RF local oscillator – which is a frequency synthesizer built around a tunable self-sustained oscillator – is also feasible.[8] Self-sustained oscillators integrated in the silicon chip tend to suffer from relatively poor short-term frequency stability, in the sense that its oscillation dephases relatively more rapidly due to the lossy (thus noisy) substances and/or constructs in the silicon chip. Nonetheless, the dephasing of any reasonably designed integrated silicon oscillators is still slow enough as compared to time scales involved in most NMR spectroscopy experiments; for instance, 0.03 RF cycle error (dephasing) after millions of RF cycles is feasible to achieve with integrated silicon oscillators.[8,17,18] Finally, the digitization of the down-converted audio-frequency signals can be also done by integrated analog-to-digital converters (ADC)[8]; because the frequency is low, the integrated ADC can achieve

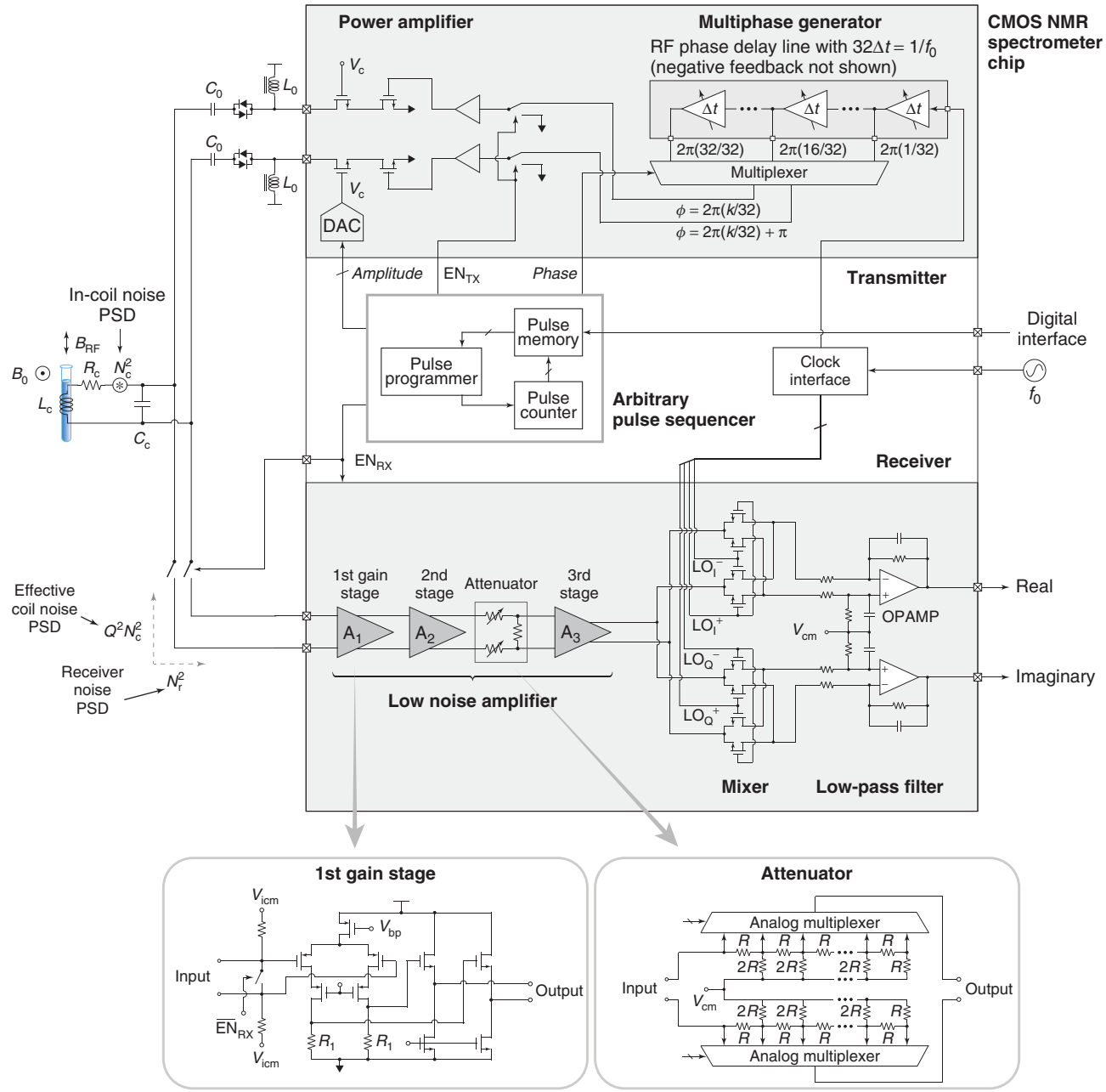

Figure 3. The circuit diagram of the silicon spectrometer chip of Figure 1(d). (Modified from D. Ha, J. Paulsen, N. Sun, Y.-Q. Song, and D. Ham, Proc. Natl. Acad. Sci. U.S.A., 2014, 111, 11955)

resolution high enough not to lose any essential information from the NMR signal.

Arbitrary Pulse Sequencer and RF Transmitter

The operations of the arbitrary pulse sequencer (Figure 3, middle) and RF transmitter (Figure 3, top) are tightly interwoven, as the former defines an RF pulse sequence and the latter delivers it to the analyte. Specifically, the arbitrary pulse sequencer turns on and off the front-end power amplifier of the transmitter, setting the duration of each RF pulse as well as the duration between neighboring RF pulses, and controls the internal circuitry of the transmitter to set the RF phase and amplitude of each pulse. As a primarily digital system, the arbitrary pulse sequencer is relatively more amenable to integration than the RF transmitter (and the RF receiver).

In our integrated implementation[9] (Figure 3), the arbitrary pulse sequencer consists of a 4096-bit refreshable memory that stores a set of digital codes representing a particular RF pulse sequence and a digital control unit that reads the memory data and accordingly controls the RF transmitter so that it can send out the specific RF pulse sequence to the coil. More concretely, the amplitude of each RF pulse is determined by altering the internal resistance inside the power amplifier. On

the other hand, the RF phase of each pulse is determined first by preparing a 2π RF phase delay line fed by the RF local oscillator (the total phase delay of the 2π through the entire line is ensured by a negative feedback) and second by tapping the RF signal off a node on the delay line with a desired phase delay (which is larger than 0 and smaller than 2π); the tapped RF signal with the desired phase then drives the power amplifier. This phase selection unit in the transmitter is indicated as multiphase generator in Figure 3.

The target RF magnetic field amplitude inside the coil determines the RF current (thus RF power) to be delivered into the coil by the transmitter. For instance, our work with the 0.51 T Halbach magnet with ^{1}H Larmor frequency of 21.8 MHz[9] (Figure 2) has a target RF field strength of 40 kHz (or a π/2-pulse duration of 6.3 μs) for ^{1}H spins. To produce this RF field with the solenoidal coil used (diameter ∼1.6 mm, length ∼1 mm, $L_c = 173$ nH, $R_c = 0.75\ \Omega$) with a sample volume of 0.8 μl, we drive the coil with an RF current amplitude of ∼251 mA, and this corresponds to a transmitted RF power of 23.7 mW. This level of power can be readily produced by the integrated power amplifier. In fact, our chip, although not designed for high RF power transmission, can still deliver a maximum RF power of 182 mW to produce an RF field strength of ∼111 kHz. Even a higher RF power can be transmitted by employing larger transistors in the integrated power amplifier, where the associated heat production can be minimized using a power-efficient amplifier topology such as tuned switching amplifier.

Spectrometer Chips at Work

Using the silicon spectrometer chips (Figure 1d) with the 0.51 T NdFeB Halbach magnet (^{1}H NMR frequency: 21.8 MHz) (Figure 2), we performed a broad range of multidimensional NMR spectroscopy experiments, which we originally reported in Ref. 9. Here, we review some of these experiments to demonstrate the integrated spectrometer chips at work. For these experiments, a capillary tube was used to hold sample, with a solenoidal coil wrapped around the tube. With the tube inner diameter of 1 mm and length inside the coil of 1 mm, the sample volume was 0.8 μl, which is two orders of magnitude smaller than the typical sample volume in a standard 5 mm

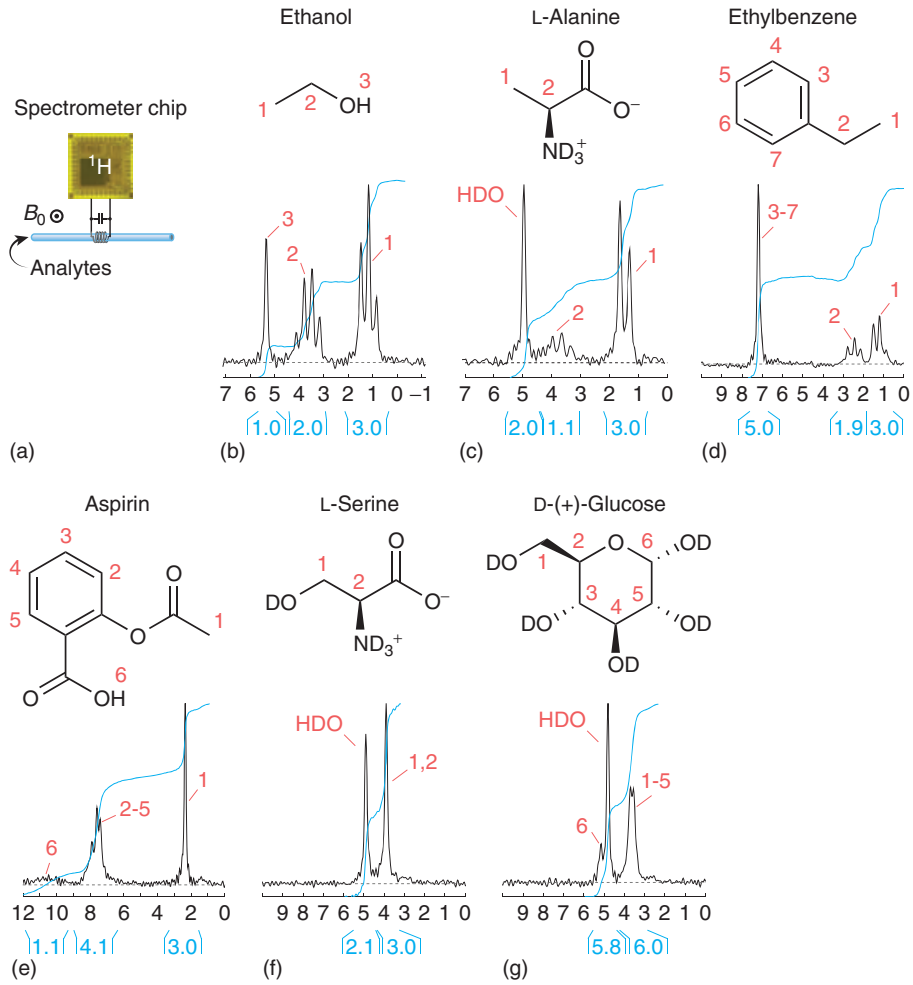

Figure 4. 1-D NMR spectra obtained with the system of Figure 2. This figure is a variation of a figure reported in Ref. 9. (a) Illustration of the experimental setup. (b–g) 1-D spectra for various molecules specified in the figure. (Modified from D. Ha, J. Paulsen, N. Sun, Y.-Q. Song, and D. Ham, Proc. Natl. Acad. Sci. U.S.A., 2014, 111, 11955)

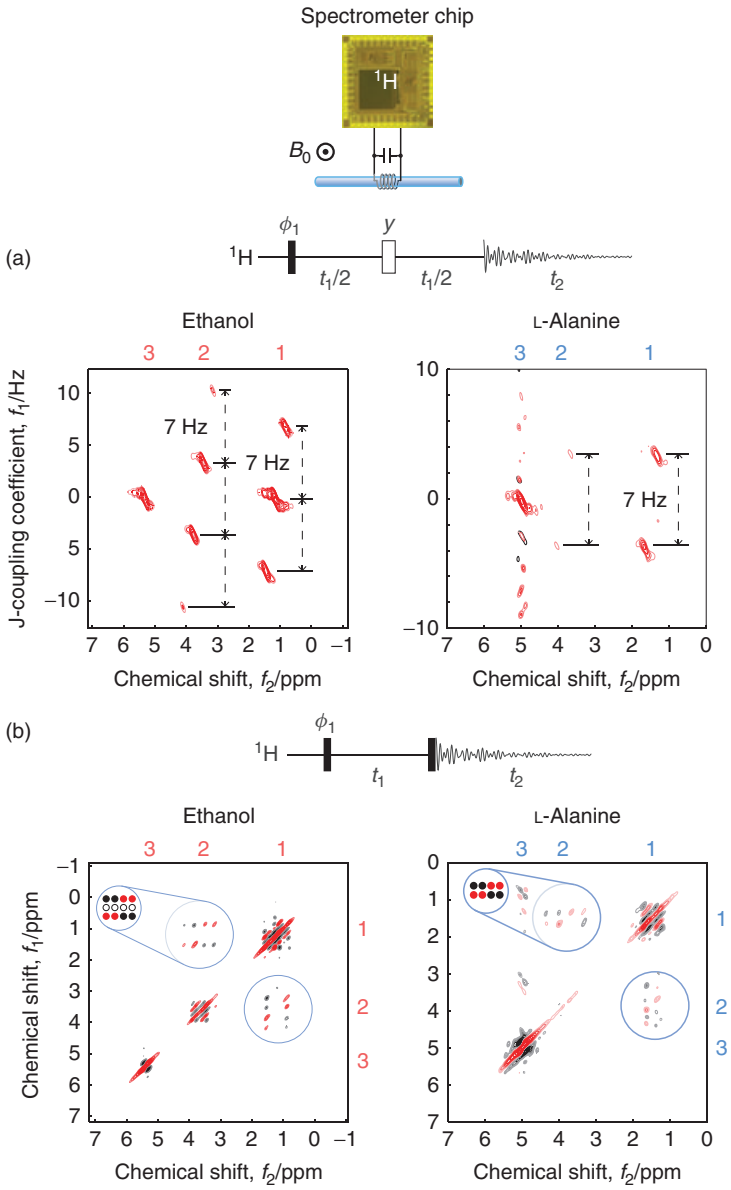

Figure 5. 2-D NMR spectra for ethanol and L-alanine, obtained with the system of Figure 2. This figure is a variation of a figure originally reported in Ref. 9. (a) *J*-resolved 2-D spectra. (b) COSY spectra with theoretical peak shapes illustrated inside the circled areas; the red and black circles signify positive and negative absorption line shapes, respectively; empty circles represent no peaks. (Modified from D. Ha, J. Paulsen, N. Sun, Y.-Q. Song, and D. Ham, Proc. Natl. Acad. Sci. U.S.A., 2014, 111, 11955)

NMR tube. The compact permanent magnet had a 0.13 ppm (2.8 Hz) field inhomogeneity after shimming. The temporal field drift of this magnet due to temperature fluctuation was calibrated out by signal processing,[9] which we will not discuss here as it is beyond the scope of this article. As these experiments were done with the low-field permanent magnet, the analytes were only small molecules.

As shown in Figure 4, our system acquires the well-established 1-D ^{1}H NMR spectra. In addition, some of these signals exhibit expected fine splittings due to J-couplings.

For a further look into the J-couplings, we performed *J*-resolved and COSY ^{1}H 2-D NMR experiments on ethanol and L-alanine (Figure 5a and b), which once again produced the expected 2-D spectra. For instance, the *J*-resolved ethanol 2-D spectrum (Figure 5a, left) exhibits ~7 Hz vertical peak splittings at each of the horizontal CH_3 and CH_2 chemical shifts. For another example, the off-diagonal cross-peak multiplets and their detailed patterns in the COSY ethanol spectrum (Figure 5b, left) once again unambiguously identify the J-coupling between the CH_3 and CH_2 groups, agreeing with detailed theoretical predictions.

Figure 6 presents two-channel (^{1}H, ^{13}C) 2-D experiments, where two spectrometer chips are synchronously operated. Specifically, HSQC and HMQC spectroscopy experiments are performed on 99%-enriched ^{13}C methanol ($^{13}CH_3OH$) to identify the ^{13}C–^{1}H J-coupling in the CH_3 group. One

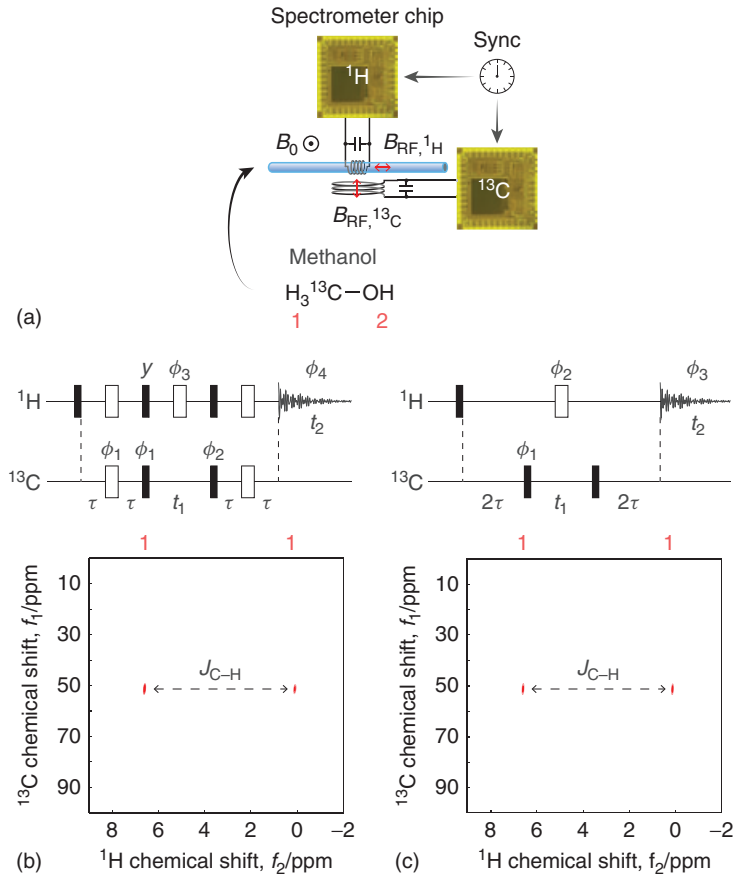

Figure 6. Heteronuclear correlation spectroscopy for ^{13}C-enriched methanol, obtained with the system of Figure 2 (with two chips). This figure is a variation of a figure originally reported in Ref. 9. (a) Illustration of the experimental setup. (b) HSQC spectrum. (c) HMQC spectrum. (Modified from D. Ha, J. Paulsen, N. Sun, Y.-Q. Song, and D. Ham, Proc. Natl. Acad. Sci. U.S.A., 2014, 111, 11955)

spectrometer chip is tuned at the ^{1}H frequency (21.8 MHz), and with its corresponding solenoidal coil wrapped around the capillary tube, it excites and records the ^{1}H signals; the other chip tuned at the ^{13}C frequency (5.2 MHz) is used for excitation only, and its corresponding coil is placed in an orthogonal orientation to the ^{1}H coil (alternatively a single doubly tuned coil can be used[19]) (Figure 6a). In each of the HSQC and HMQC spectra (Figure 6b and c), which are obtained by using both ^{13}C and ^{1}H channels for excitation (for quantum coherence manipulation and transfer) while using only the ^{1}H channel for recording, two peaks separated by 140 Hz along the ^{1}H chemical shift appear at the same ^{13}C chemical shift, revealing the ^{13}C–^{1}H single-bond coupling, while the OH proton uncoupled to carbon does not exhibit a signal.

These experiments clearly highlight some of the benefits of integrated spectrometer chips. First, the *overall* portable NMR spectroscopy system for small-molecule analysis is indeed possible by complementing the recent advance in the NMR-grade permanent magnet construction[10,12,13] with the spectrometer electronics integration; such portable systems can be used for on-site or online analysis of small molecules for such applications as chemical reaction monitoring and quality control.[11] Second, the demonstrated heteronuclear NMR spectroscopy experiments show how greatly the small spectrometer chips simplify multichannel experimental setup in a compact configuration. Such simplicity can be taken advantage of in various other multichannel experiments, such as phased-array applications[20,21] and multichannel microscopic flow monitoring.[22]

In addition, although not demonstrated, we envision that massively parallel NMR spectroscopy is possible by running a large number of independent spectrometer chips on their respective coils/analytes inside a superconducting magnet. For example, multiple analytes of different types can be analyzed in parallel. Or multiple analytes of the *same* type can be analyzed with each sample assigned to a different indirect evolution time t_1, which could enable 2-D NMR for the given type of analyte in one single parallel scan. No matter what the detailed operational protocol is, such parallelism can help circumvent the fundamental slowness of individual NMR spectroscopy experiments in order to achieve the high-throughput paradigm, which is much desired for macromolecular applications in structural biology and pharmaceutical screening. Such parallelization is a far cry from being trivial, requiring careful optimizations of position-dependent local field homogeneity inside a superconducting magnet and minimization of interferences across sample/coil/chip sites. Yet, such parallelization

would be daunting with the conventional bulky spectrometer electronics, while it can be now more practically considered with the integrated spectrometer chips due to their small size and low cost.

Conclusions

This article reviewed the recent development of integrated multidimensional NMR spectrometer chips and their demonstrated benefits as well as potential impacts in the science and technology of NMR. Silicon chips have played a central role in the information technology revolution, as they can be fabricated inexpensively while integrating vast electronic functions in their small footprints. Recent years have witnessed a wealth of efforts to exploit this small-cost, small-size advantage of silicon chips beyond information technology, in particular, to analyze chemical analytes, biological molecules, cellular dynamics, and living organisms (one notable example is the *tour-de-force* demonstration of all-electronic DNA sequencing with silicon chips[23]). It is this broad emerging theme under which the next-generation NMR spectroscopy system based on silicon chips and new exciting possibilities it might enable may be considered.

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Related Articles

Microcoils; Mobile Nuclear Magnetic Resonance; Receiver Design for MR; Spectrometers: A General Overview; Impedance Matching and Baluns

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