

Silicon RF NMR Biomolecular Sensor — Review

(Invited Paper)

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Abstract—This paper reviews our first miniature nuclear magnetic resonance (NMR) system originally reported in [1], [2], which, weighing only 2 kg, is 60 times lighter, 40 times smaller, yet 60 times more spin mass sensitive than a 120-kg state-of-the-art commercial benchtop NMR system. The miniaturization was made possible by combining the physics of NMR with a high-performance CMOS radio-frequency integrated circuit. The system is aimed at sensing biomolecules such as cancer marker proteins, and represents a circuit designer’s approach to pursue low-cost diagnostics in a portable platform. Our most recent development of even smaller NMR systems [3] will not be reviewed here, as it has yet to be exposed in full through a journal publication first.

I. INTRODUCTION

In recent years we have developed three miniature nuclear magnetic resonance (NMR) systems in decreasing size [1]–[3], which are orders-of-magnitude smaller than the state-of-the-art commercial benchtop NMR system [4]. The works were made possible by combining the physics of NMR with CMOS radio frequency (RF) integrated circuits (ICs). The small NMR systems can be used for biomolecular sensing aimed at low-cost disease screening.

The purpose of this invited paper is not to report on a new work, but to review our *first* miniature NMR system shown in Fig. 1 [1], [2], the largest among the three systems yet the first step towards the miniaturization, and its application in biomolecular sensing. We will leave out our latest development of the other two systems that are even smaller [3], as these works still need to be exposed in full through a journal publication first. This paper, as a review, will extensively borrow materials from our earlier publication in [1] that reported on the first miniature NMR system.

When disease develops, biomolecules characteristic to the disease, such as disease marker proteins, emerge in blood or urine. The ability to sense these biomolecules would facilitate disease detection. In pursuit of such benefits for human health-care, researchers from many areas of science and engineering are developing a variety of biosensors. Our CMOS RF NMR biosensor may be viewed as a circuit designer’s way to pursue low-cost diagnostics in a portable platform.

The underpinning physical phenomenon of our biomolecular sensing method is nuclear magnetic resonance (NMR). NMR is an energy exchange between RF magnetic fields and atomic nuclei, such as hydrogen protons, which act like tiny bar magnets due to their spins. The presence of target biological objects in an aqueous sample alters the dynamics

of hydrogen protons, which can be detected by performing an NMR experiment. This NMR-based biosensing method was developed in 2002 [5] and had been performed using a state-of-the-art commercial benchtop NMR system [4], which is bulky and heavy (120 kg).

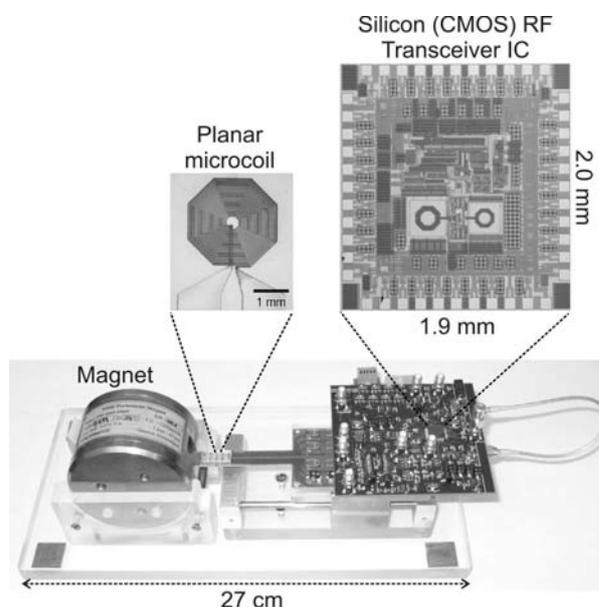


Fig. 1. Our first miniature CMOS RF NMR biosensor. Reprinted from [1], [2]

Our first miniature NMR system [Fig. 1] occupies only 2.5 liters and weighs only 2 kg. As compared to the state-of-the-art commercial benchtop NMR system, it is 60 times lighter, 40 times smaller, yet 60 times more mass sensitive. To achieve this drastic miniaturization, we took an approach opposite the convention. The usual way to construct an NMR system, consisting of a magnet, a sample coil, and a transceiver, is to use a large magnet to produce a strong NMR signal (larger-sized magnet yields stronger NMR signal, even with the same magnetic field), hence relaxing the sensitivity requirement on the transceiver design, but leading to the bulky NMR instrumentation. In contrast, to shrink the system size, we opted to use a small magnet the size of a hamburger [Fig. 1]; and to detect the NMR signal substantially weakened by the small magnet, we designed a high-performance CMOS RF transceiver and a separately micro-fabricated coil. As a biosensor, the mini NMR system detected down to 20 fmol, 1.4

ng avidin (protein) in a 5- μ L sample volume. This detection threshold can be even further improved, for it is currently not limited by our transceiver sensitivity, but by the specific bioassay used [6], [7].

II. CMOS RF TRANSCEIVER IC DESIGN

A. Transceiver Architecture

The architecture of our CMOS RF transceiver is shown in Fig. 2. The transceiver excites an NMR sample placed on the planar microcoil [Fig. 1], then subsequently receives a response NMR signal from the sample/coil system. The coil is modeled as an inductor, $L = 500$ nH, in series with parasitic resistance, $R = 4.2\Omega$ [Fig. 2, right].

Suppose an NMR experiment on hydrogen protons in an aqueous sample. The sample is placed on top of the microcoil, which altogether is subjected to a DC magnetic field $B_0 \sim 0.5$ T from the hamburger-sized magnet [Fig. 1]. Subsequently, the transmitter [Fig. 2, upper half] sends in an RF signal to the coil, which produces an RF magnetic field inside the sample. Hydrogen protons in the sample are nucleic magnets, and when subjected to B_0 , they have a characteristic frequency: $\omega_L/2\pi = 42.6 \cdot B_0 = 21.3$ MHz. If the RF magnetic field's frequency is ω_L , it resonantly excites the proton magnets. After a while, the RF transmission is ceased, and the receiver is turned on [Fig. 2, lower half]. From this point, the excited proton magnets electromagnetically interact with the coil, inducing an AC voltage signal across the coil. This NMR signal, appearing at node ② after the matching network, is a weak signal (available power: 0.5 fW) centered at ω_L with a narrow bandwidth of 1 kHz. It is detected by the heterodyne receiver.

We set the intermediate frequency (IF) of the heterodyne receiver, δ at node ③, to be 3 kHz. This is high enough to mitigate the mixer $1/f$ noise, yet low enough to facilitate the rejection of the out-of-band noise by placing a band-pass-filter at the mixer output. For frequency down-conversion, two mixers driven by quadrature oscillator signals are used. The two outputs from the mixers are digitized by an off-chip ADC and subsequently processed by an off-chip signal processing unit to perform image rejection. This image rejection is to avoid the extra 3 dB degradation in the noise figure (NF) due to the frequency down conversion.

We use one clock source [Fig. 2, left] to produce both the excitation signal in the transmitter and the local oscillator (LO) signal in the receiver, instead of using two separate clocks. The frequency of our single clock is set at a value 3 kHz larger than $\omega_L/2\pi$ so as to produce the IF of 3 kHz. Therefore the excitation signal at node ① is not at ω_L , but it can still excite protons, because the signal transmission time is finite, thus, the excitation signal has a non-zero bandwidth that is large enough to include ω_L in it. The advantage of this one-clock scheme is its simplicity: we only need to tune the frequency of one clock instead of tuning two clocks separately while keeping their frequency difference to be 3 kHz.

The digital pulse generator is to produce various NMR pulse sequences (e.g., the CPMG pulse sequence [8]), which

is crucial in practical NMR experimentations.

B. Receiver Design

Fig. 3 shows the detailed schematics of the heterodyne receiver, which is comprised of a low noise amplifier (LNA), a variable gain amplifier (VGA), and a double-balanced Gilbert mixer. When PA is driving the coil, a large excitation signal appears at the LNA input. In order to protect the receiver from entering saturation under this situation, we use switches $S_1 \sim S_6$ to short the load of the LNA and the VGA, and disconnect the LNA, the VGA, and the mixer.

The LNA is a fully-differential common-source amplifier with common-mode feedback. To detect the weak NMR signal (peak-to-peak: ~ 100 nV), it is critical to design a highly sensitive LNA with as low a noise figure (NF) as possible. To minimize the NF, not only the LNA's input referred noise should be minimized, but also an optimum noise matching should be provided between the LNA and the NMR coil.

First, to minimize the input referred noise of the LNA, we take the following measures: i) PMOS devices are chosen as input devices to minimize $1/f$ noise and substrate coupling from digital circuits; ii) a large tail current (4 mA) and wide input transistors (900 μ m) are used to boost g_m and hence lower the channel thermal noise; iii) the load transistors are biased with a large overdrive voltage to reduce their noise contribution; iv) cascode transistors are added to attenuate coupling between the local oscillator and the LNA. From SPICE simulation, the input referred noise of the LNA at ω_L of 21.3 MHz is 1.3 nV/ $\sqrt{\text{Hz}}$ and its voltage gain is 41 dB.

Second, for the optimum LNA-coil noise matching, we place a capacitor C_m in parallel with the coil [Fig. 3, right], where C_m resonates with the coil inductance L at ω_L . This resonance network passively amplifies both the signal and the noise from the coil with voltage gain of $Q = 16$, where Q is the coil quality. As C_m has negligible loss as compared to the coil, this passive amplification introduces inappreciable extra noise. It enhances both the signal and noise from the coil beyond the LNA's input referred noise, and thus, signal-to-noise-ratio (SNR) is minimally degraded by the LNA, leading to minimum NF.

The VGA is to handle various signal levels and ensure receiver linearity. It is a fully-differential amplifier with tunable loads shown within the two dashed boxed [Fig. 3]. As the control voltage V_C increases from 0 to V_{dd} , the active loads undergo transitions from cut-off to pinch-off to triode, leading to decreasing output impedances and gain. By setting up different transitions points in the three branches and combining them in parallel, the overall load impedance is tuned more smoothly over a wider range of V_C as compared to the case of any single branch is used alone. The gain tuning range of this VGA is from 0.8 to 22.

The double-balanced Gilbert mixer with active loads exhibit a gain of 26 dB. Cascode transistors are added to mitigate the undesired feed-through from the local oscillator to the LNA's input path.

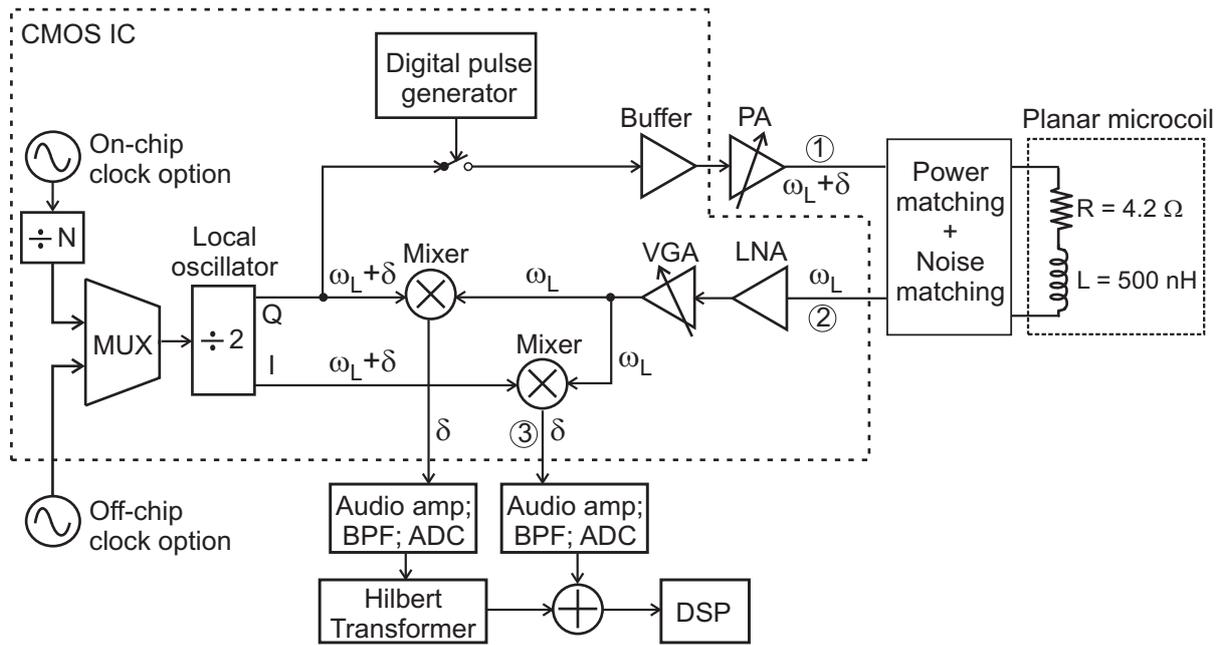


Fig. 2. NMR RF transceiver IC Architecture. Reprinted from [1].

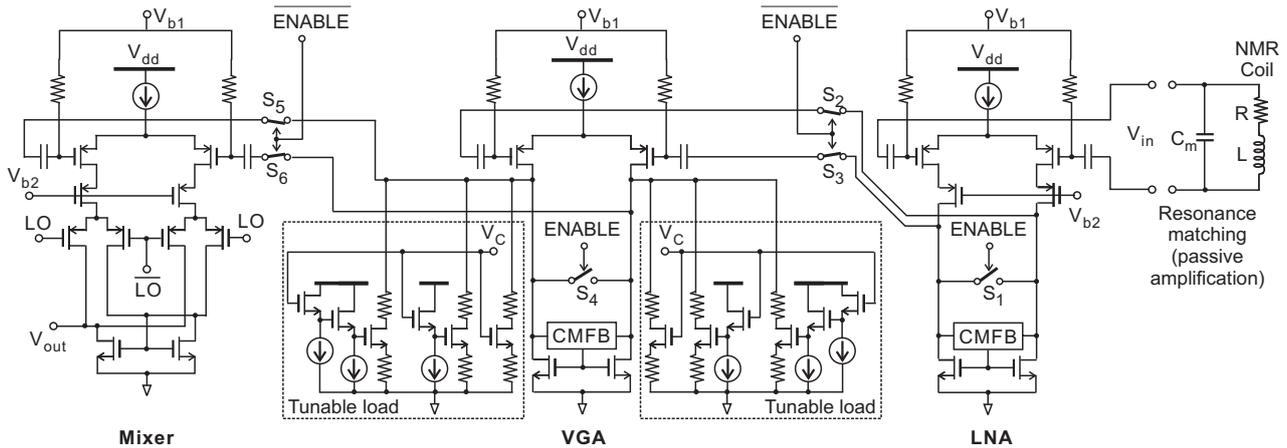


Fig. 3. The receiver chain. Reprinted from [1].

III. EXPERIMENTS

The NMR transceiver chip [Fig. 1] was implemented in 0.18- μm CMOS technology. As we deal with weak NMR signals, the most important aspect of our design is the receiver NF, which we obtained by directly measuring the receiver input referred noise. After feeding an RF signal to the receiver input (node ②, Fig. 2), we measured the output at node ③ using a spectrum analyzer. From this, we extracted the gain and the output noise of the receiver. By dividing the output noise by the gain while factoring out the image noise, which is taken care of by the image rejection architecture [Fig. 2], we obtained the input referred noise of 1.8 $\text{nV}/\sqrt{\text{Hz}}$. It is larger than the SPICE-simulated value of 1.3 $\text{nV}/\sqrt{\text{Hz}}$, for noise from the power supply and substrate are not taken into account in

the simulation. From the measured input referred noise and measured impedance of the coil, we obtain the noise figure of the receiver. Thanks to the resonance noise matching [Fig. 3, right], the overall NF is only 0.7 dB.

We assembled the entire NMR system of Fig. 1 by putting together the RF IC with auxiliary electronics on the printed circuit board, along with the hamburger-sized commercially-available magnet and the planar microcoil fabricated using standard photolithography. A 5- μL aqueous sample is held on the microcoil inside a microfluidic container mounted on top.

Fig. 4, top shows the measured down-converted NMR signal in a water proton NMR experiment. The ringings, result of a specific transmitted pulse sequence (the CPMG pulse sequence [8]), are the NMR signal. It decays with a characteristic time,

T_2 , which reflects the sample's internal dynamics and is a key quantity in our NMR-based biomolecular sensing [5], as will be seen shortly. From the exponentially decaying envelope of the signal, shown as the dotted line, $T_2 = 523$ ms is extracted. The repeated large spikes are the coupling of the transmitted excitation signal, but they do not compromise the observation of the conspicuous NMR signal, as they occur at different time instances.

The physics of NMR prescribes that T_2 decreases if magnetic nanoparticles [Fe] are suspended in the water. Figure 4, bottom, shows that when 0.17 mM magnetic nanoparticles (30 nm) are added into the water, the measured T_2 decreases to 60 ms. We also tested our system for various magnetic nanoparticle concentrations. Experiment results show that the T_2 decreases proportionally as the nanoparticle concentration increases, which conforms to the NMR theory, affirming our system's functionality.

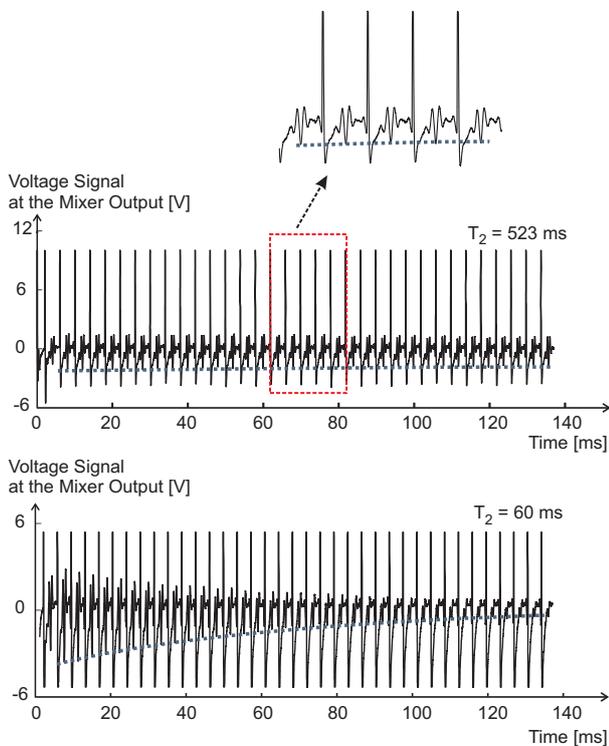


Fig. 4. Measured, down-converted echo signals: (top) pure water; (bottom) water with magnetic nanoparticles (0.17 mM). Reprinted from [1], [2].

We used our system to detect various biomolecules. Figure 5 shows one example, the detection of avidin protein. Magnetic nanoparticles coated with biotins are put into a 5- μ L aqueous sample. In the absence of avidin [Fig. 5, top], the particles stay mono-dispersed, yielding $T_2 = 73$ ms. When avidin exists in the sample, the magnetic particles self-assembled into clusters around the avidin proteins [5], reducing T_2 to 31 ms [Fig. 5, bottom]. The reduction of T_2 indicates the presence of avidin. The minimum detectable quantity of avidin was 20 fmol and 1.4 ng in the 5- μ L sample volume. In comparison to the state-

of-the-art commercial benchtop NMR system [4], our system is 60 times more sensitive in terms of the absolute detectable quantity.

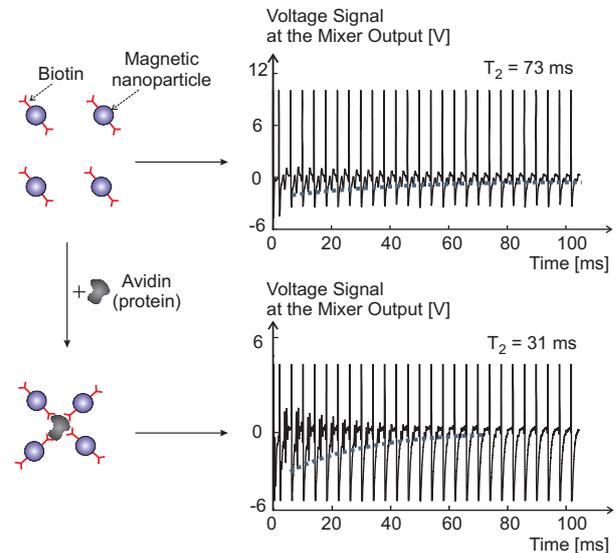


Fig. 5. Experimental avidin detection. Reprinted from [1], [2].

IV. CONCLUSION

In this paper, we reviewed our first miniature NMR system that was originally reported in [1], [2]. The miniaturization was enabled by combining the physics of NMR with CMOS RF integrated circuits. The NMR system, which can be used for sensing biological molecules in the low-cost portable platform, is an addition to the arsenal of biomolecular sensors being developed for diagnostics purposes.

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