

27.2 Palm NMR and One-Chip NMR

Nan Sun¹, Tae-Jong Yoon², Hakho Lee², William Andress¹,
Vasiliki Demas³, Pablo Prado³, Ralph Weissleder², Donhee Ham¹

¹Harvard University, Cambridge, MA,

²Massachusetts General Hospital, Harvard Medical School, Cambridge, MA,

³T2 Biosystems, Cambridge, MA

Nuclear magnetic resonance, or NMR, is the energy exchange between an RF magnetic field and an atomic nucleus such as a hydrogen proton, which is a tiny bar magnet due to its spin. NMR has a broad array of powerful applications, including: biomolecule sensing (e.g., cancer marker detection), medical imaging, and oil detection. NMR instruments, however, are bulky, heavy, and expensive, and remain as specialized equipment in hospitals, industry, and laboratories. An NMR system consists of a magnet, a sample coil, and an RF transceiver, where the magnet is by far the largest component. As a larger-sized magnet yields a stronger NMR signal even for the same field strength, large magnets are used, hence the bulky size.

Small NMR instruments with low cost would bring the benefits of NMR closer to our lives. For example, a miniature NMR biosensor may enable cancer screening in a doctor's office or a patient's home at an affordable cost. In [1,2], we reported a 2kg 'portable' NMR system that was 60x lighter, 40x smaller, yet 60x more spin-mass sensitive than a 120kg state-of-the-art commercial system [3]. To achieve this, we took an approach opposite the convention: we used a small magnet the size of a hamburger (0.49T), and to detect the NMR signal weakened by the small magnet, we designed a partially integrated, high-performance RF transceiver and a separate coil.

In this paper we report on two NMR systems that represent yet another orders-of-magnitude size reduction and lab-on-a-chip capabilities. First, we report a 0.1kg 'palm' NMR system (Fig. 27.2.1). It is 20x lighter, 30x smaller, yet 2.5x more spin-mass sensitive than our prior 2kg portable NMR system of [1,2]. As compared to the 120kg commercial system, the palm system is 1200x lighter, 1200x smaller, yet 150x more spin-mass sensitive. Production cost reduction is 1400x. To achieve this further orders-of-magnitude size reduction, we use a tiny magnet the size of a ping-pong ball (0.56T) (Fig. 27.2.1). This significantly lowers the NMR signal power, which we overcome by designing a new RF transceiver fully integrated in 0.18μm CMOS. Our prior work [1,2] did not integrate a power amplifier (PA), since meeting the large power tuning requirements of NMR is difficult with an integrated PA. In this work, a transmitter technique exploiting an atomic nuclei's natural high-Q (~10⁴) filtering ability enables an integrated PA. As the signal is already lowered by the ping-pong-ball-sized magnet, the palm system uses a high-quality solenoidal coil, in order not to further weaken the signal.

Second, we report a '1-chip' NMR system (Fig. 27.2.2), where even the coil, as a planar spiral, is integrated with the new CMOS RF transceiver. While a few such 1-chip systems have been reported (e.g., [4]), integration levels were far lower and they worked with far larger magnets. Performance of our transceiver permits the use of the lossy on-chip coil. As the signal is already weak owing to the on-chip coil, the 1-chip system operates with the hamburger-size magnet of our prior work [1,2], not to further reduce the signal. Due to this magnet, the weight reduction from [1,2] is by 25%, but the point of the 1-chip system is its *lab-on-a-chip* operation, interfacing a sample directly with the chip. For example, a blood sample can be placed on the coil part of the chip for on-chip disease screening. The chip can be used as a disposable device for one-time diagnostic testing. The direct interface may also enable practical quantum computing and oil detection on CMOS chips. This system has the same spin-mass sensitivity as [1,2], and is 60x more spin-mass sensitive than the commercial system.

Another contribution is biomolecule sensing relevant to disease screening using these systems. We detect human chorionic gonadotropin (hCG) protein, a marker for cancers such as choriocarcinoma and germ cell tumor, and detect human bladder cancer cells.

Figure 27.2.3 shows the CMOS RF transceiver, with the off-chip solenoidal coil (palm system) and on-chip planar coil (1-chip system). A sample (e.g., blood) placed in/on the coil is subjected to the static magnetic field B_0 of a magnet. Hydrogen protons in the aqueous sample are nucleic magnets with NMR frequency $\omega_0/2\pi=42.6B_0$ (palm: 23.9 MHz; 1-chip: 21.3MHz). The transmitter produces an RF magnetic field in the coil. If its frequency is ω_0 , it excites proton magnets. When the RF transmission ceases, excited proton magnets induce an AC voltage (frequency ω_0) across the coil. The heterodyne receiver detects this NMR signal. IF is 3kHz. This is high enough to mitigate 1/f noise, yet low enough to reject out-of-band noise.

The integrated transmitter (Fig. 27.2.4) uses a class-D PA consisting of differential chains of inverters. They are consecutively quadrupled in size to sequentially amplify power and ensure drivability. In transmission mode, a large output-power tuning range is needed to control the proton excitation rate. For this, we tune the duty cycle of a square-wave RF excitation signal (frequency ω_0 ; amplitude V_{DD}). For a given duty cycle, the square wave has a particular power distribution of harmonics. The harmonic distribution varies with duty cycle. Only the ω_0 component matters, since higher harmonics lie outside the 'proton filter' band: protons are a high-Q (~10⁴) filter centered at ω_0 , as they are not excited outside the band. As duty cycle changes from 0 to 50%, the ω_0 component changes from 0 to 0.63 V_{DD} . This leads to output power tuning. The input to the duty-cycle controller (Fig. 27.2.4) is a square wave (ω_0 ; V_{DD}) with 50% duty cycle. An AND operation on this and its delayed version yields a duty cycle that varies with the delay. As delay changes from 0 to π/ω_0 , the duty cycle shifts from 50 to 0%. The delay is tuned by using 3 voltage-controlled inverters in parallel. Inv-1 is a current-starved inverter. Its delay is not linear with control voltage V_C . Inv-2, a complementary current-starved inverter, prevents the steep delay increase for small V_C . Inv-3, a current-starved inverter with a source follower, sustains a delay reduction with increasing V_C . The overall delay tuning is linear.

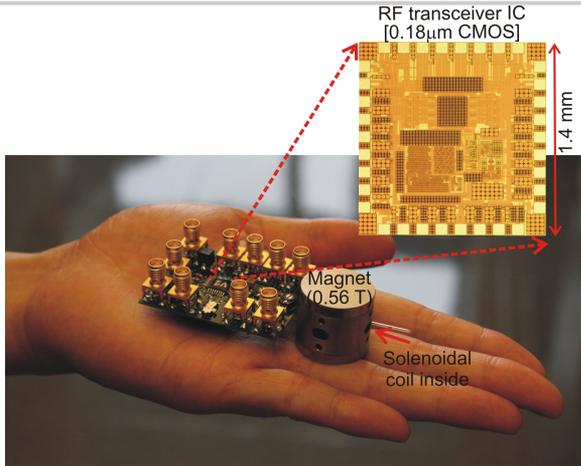
The heterodyne receiver (Fig. 27.2.5) consists of an LNA, a VGA, and a mixer. The receiver is fully differential in implementation. We minimize the LNA's input-referred noise (measured value: 1.6nV/Hz^{1/2}) by taking several measures: (1) PMOS devices are used as input devices to minimize 1/f noise and substrate coupling from digital circuitry; their sizes are maximized within constraints to mitigate drain thermal noise; (2) cascode transistors attenuate leakage of the local oscillator to LNA input; (3) resistive loads are used to obviate the need for common-mode feedback; as resistive loads produce lower gain, a 2-stage amplifier is used. To minimize noise figure (NF), optimum LNA-coil matching is also needed. It is obtained with capacitor C_m in parallel with the coil (Fig. 27.2.5) where C_m resonates with coil inductance L at ω_0 . This *passively* amplifies signal & noise with voltage gain $(Q^2+1)^{1/2}$, where Q is coil quality. The passive amplification enhances coil signal & noise beyond the input-referred noise, and thus, SNR is minimally degraded by the LNA. In the palm system, a passive gain of 28 lowers the measured NF from 24.6dB to 1.4dB. In the 1-chip system, a passive gain of 2.1 lowers the measured NF from 7.8dB to 3.2dB.

An NMR signal decays with characteristic time T_2 . Reflecting sample's internal dynamics, it is a key quantity in NMR biosensing [5] and medical imaging. We measure T_2 with the two systems to detect biomolecules. Fig. 27.2.6 shows measurements with the palm system. Measured NMR signal (ringings) for 2μL water placed in the solenoid is in Fig. 27.2.6 (top). $T_2=100$ ms from their decaying envelope. Magnetic particles (38nm) coated with biotins are put in the water. In absence of avidin (Fig. 27.2.6, middle), the particles stay mono-dispersed. They perturb NMR dynamics, reducing T_2 to 48ms. In the presence of avidin (Fig. 27.2.6, bottom), the biotinylated particles bind to avidin, forming clusters [5]. These perturb NMR dynamics more, further reducing T_2 to 40ms. The T_2 change detects avidin. The spin-mass sensitivity is 2.5x higher than our prior work [1,2], and 150x higher than the commercial system.

Figure 27.2.7(a) shows hCG cancer-marker detection with the 1-chip system. Magnetic particles (38nm) coated with mouse monoclonal antibody to hCG are put into 5μL water placed on the planar coil. $T_2=169$ ms in absence of hCG; $T_2=141$ ms in its presence. This represents hCG detection. The system is capable of sensing 1 hCG molecule in 12 billion water molecules. Fig. 27.2.7(b) shows detection of human bladder cancer cells from the HT1197 cell line (ATCC) with the same system. The detection threshold is 17.5cells/μL. The spin-mass sensitivity is the same as our prior work [1,2], and 60x higher than the commercial system.

References:

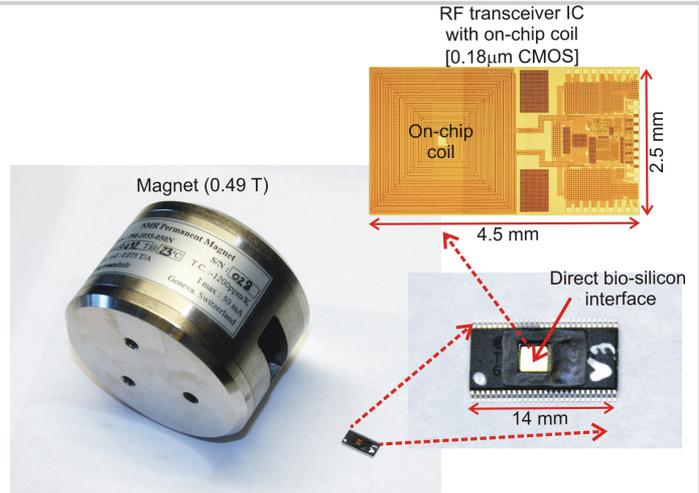
- [1] Y. Liu *et al.*, "CMOS Mini Nuclear Magnetic Resonance System and its Application for Biomolecular Sensing," *IEEE ISSCC Dig. Tech. Papers*, pp. 140-141, Feb., 2008.
- [2] N. Sun *et al.*, "CMOS RF Biosensor Utilizing Nuclear Magnetic Resonance," *IEEE J. Solid-State Circuits*, vol. 44, no. 5, pp. 1629-1643, May 2009.
- [3] Bruker Optics, "The minispec TD-NMR Analyzers," 2009, accessed December 5, 2009, <<http://www.brukeroptics.com/minispec.html>>.
- [4] G. Boero *et al.*, "Fully Integrated Probe for Proton Nuclear Magnetic Resonance Magnetometry," *Rev. Sci. Instruments*, vol. 72, pp. 2764-2768, Jun., 2001.
- [5] J. M. Perez *et al.*, "Magnetic Relaxation Switches Capable of Sensing Molecular Interactions," *Nature Biotechnology*, vol. 20, pp. 816-820, Aug., 2002.



Palm NMR system (0.1 kg)

- 20x lighter, 30x smaller, 2.5x more spin-mass sensitive than [1,2]
- 1200x lighter, 1200x smaller, 150x more spin-mass sensitive than the state-of-the-art commercial NMR system

Figure 27.2.1: Palm NMR system.



1-Chip NMR system (Lab-on-a-chip)

- Direct interface between bio-sample and IC
- Disposable sensor probe with on-chip coil

Figure 27.2.2: One-chip NMR system.

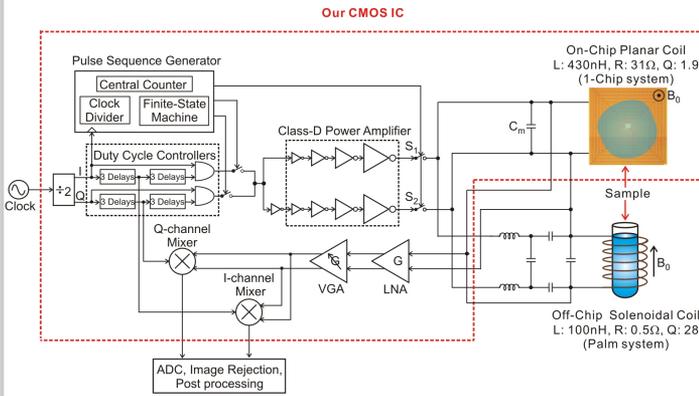


Figure 27.2.3: CMOS RF transceiver architecture.

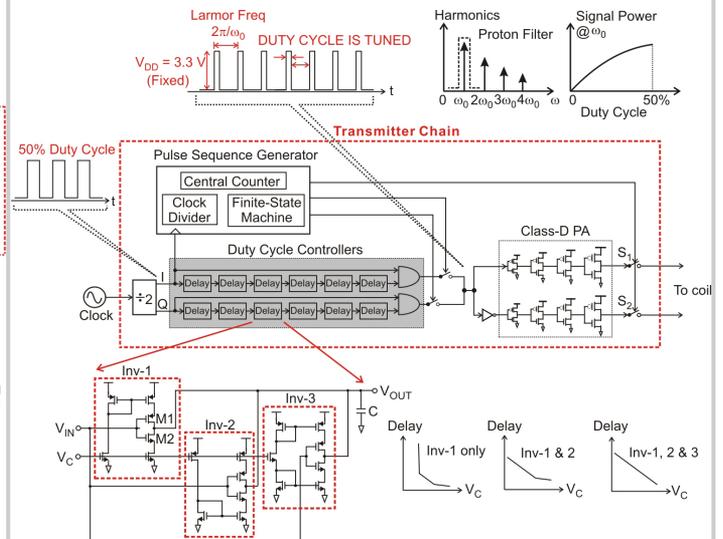


Figure 27.2.4: Transmitter chain and power tuning scheme.

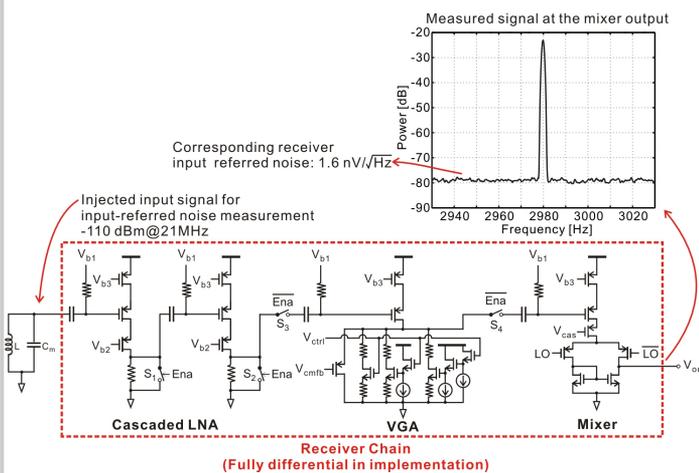


Figure 27.2.5: Receiver chain.

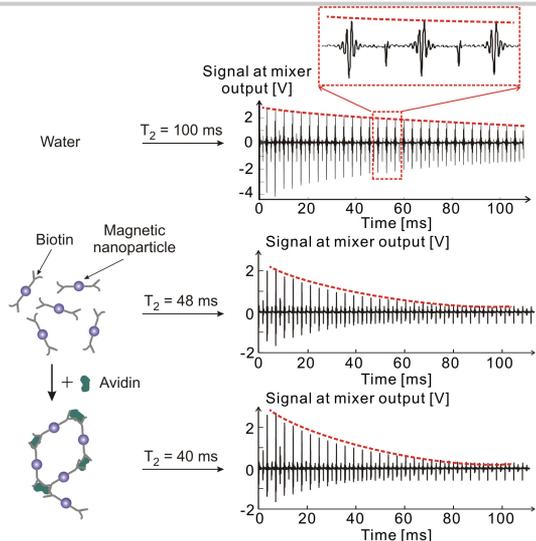


Figure 27.2.6: NMR experiments with the palm system: (top) water NMR; (middle, bottom) avidin detection using biotinylated magnetic particles.

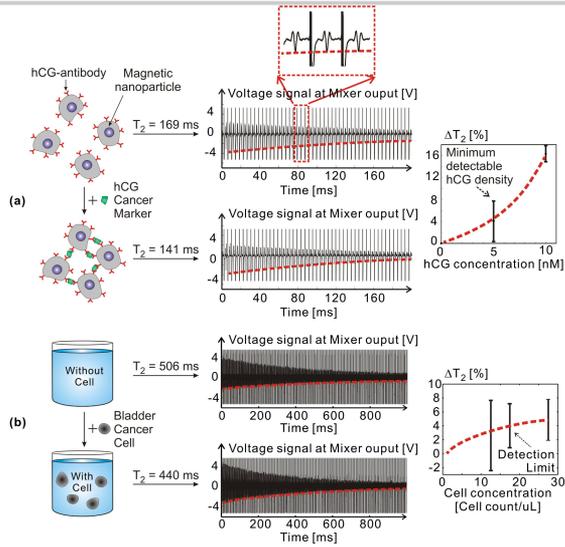


Figure 27.2.7: NMR experiments with the one-chip NMR system: (a) hCG cancer marker detection; (b) human bladder cancer cell detection.