

### 7.3 CMOS Mini Nuclear Magnetic Resonance System and its Application for Biomolecular Sensing

Yong Liu<sup>1</sup>, Nan Sun<sup>1</sup>, Hakho Lee<sup>2</sup>, Ralph Weissleder<sup>2</sup>, Donhee Ham<sup>1</sup>

<sup>1</sup>Harvard University, Cambridge, MA

<sup>2</sup>Massachusetts General Hospital, Harvard Medical School, Boston, MA

This paper reports the smallest complete nuclear magnetic resonance (NMR) system (Fig. 7.3.1), made possible by CMOS integration of a highly sensitive and versatile RF transceiver. The system's functionality is verified through proton NMR measurements in water and biomolecular sensing. The system is 60× more sensitive, 40× smaller, and 60× lighter than a commonly-used, state-of-the-art commercial benchtop NMR system [1]. Before discussing our system, let us, in one paragraph, review the NMR basics.

The basic components of an NMR system are (Fig. 7.3.2): a magnet (static magnetic field  $B_0$ ), an RF coil surrounding a sample, and an RF transceiver linked to the coil. If an RF signal with the right frequency  $\omega_0$  is transmitted to the coil (Fig. 7.3.2, top), the RF magnetic field produced by the coil resonantly excites nuclei spins within the sample (e.g., proton spins in water). Once the RF excitation is stopped after a certain time by switching the coil to the receiver (Fig. 7.3.2, bottom), spins will precess about the  $B_0$ -axis at the frequency  $\omega_0$ , while slowly losing phase coherence via spin-spin interactions, which, on a macroscopic average, manifests as an exponential relaxation (damping) in the precession of the net magnetic moment. During this precession & relaxation, the coil picks up a damped sinusoid, *a.k.a.*, the NMR signal (Fig. 7.3.2, bottom). The resonance frequency,  $\omega_0 = \gamma B_0$  ( $\gamma$ : gyromagnetic ratio), and the relaxation's characteristic time, called  $T_2$ , are material specific. By measuring  $\omega_0$  (spectroscopy) &  $T_2$  (relaxometry), NMR techniques are useful for chemical analysis, medical imaging, & biosensing [2].

Let us return to our mini NMR system. Previously in [3], we reported an NMR system using in-house fabricated planar microcoils on a glass and a commercial, fist-size magnet ( $B_0=0.5T$ ), but the RF transceiver, built with discrete components, left the system bulky. The NMR system of the present paper (Fig. 7.3.1) adopts the same microcoil and magnet of [3], but takes a significant step forward with CMOS integration of the RF transceiver, substantially reducing the overall system into the smallest size reported so far.

The key challenge was to overcome the adverse conditions for NMR detection, caused by the low-quality magnetic field (weak strength & pronounced inhomogeneity) of the small magnet necessary for miniaturization. First, the weak field  $B_0$  yields a weak NMR signal. This was overcome by designing a highly sensitive receiver (Fig. 7.3.3). Second, the pronounced field inhomogeneity causes the NMR signal to be damped far faster than  $T_2$ . This makes difficult relaxometry (the true  $T_2$  due to spin-spin interaction is hard to know), even with high receiver sensitivity. To prevent the premature damping due to field inhomogeneity, our transmitter employs a digital pulse generator, which transmits the RF signal in a sequence devised by Carr & Purcell (Fig. 7.3.3): this sequence effectively offsets field inhomogeneity, and the resultant NMR signal termed *spin echoes* (Fig. 7.3.3) allows true  $T_2$  measurement. This relaxometry is our system's main function.

Significant efforts exist to miniaturize NMR systems [1,3-7], for low cost and portability. Most miniature NMR reports have so far focused on microcoils [3-7] or small magnets [3,7], but no comprehensive integration of transceivers (e.g., pulse sequence) has been undertaken as in our system. Our system is hence far smaller than any mini-NMR system reported [1, 3-7]: e.g., the widely-used state-of-the-art commercial benchtop NMR relaxometer in [1] weighs ~120kg and spans ~10<sup>3</sup>cm<sup>3</sup>; our system weighs ~2kg and spans ~2500cm<sup>3</sup>.

The transceiver architecture is shown in Fig. 7.3.3. The CMOS IC is inside the dashed box. The switch between the PA and coil steers the coil between the transmitter and receiver. The fully-differential, heterodyning receiver uses Gilbert mixers. Since our experiments here use water proton spins and  $B_0 = 0.5T$ , the NMR frequency ( $\omega_0/2\pi$ ) is ~21.3 MHz. The frequency of the local oscillator sig-

nals  $I$  &  $Q$  for heterodyning is tuned slightly off from the NMR frequency by about 1kHz. This frequency offset is large enough to avoid *dc* offset problems at mixer outputs, but small enough to reject higher frequency noise. This scheme requires frequency synthesis with 1kHz resolution at the local oscillator. The chip has provisions for both on- and off-chip oscillators. The same  $I$  &  $Q$  signals used in the receiver are used as RF excitation signals in the transmitter of Fig 7.3.3. The aforementioned slightly-off excitation frequency is close enough to  $\omega_0/2\pi$  to excite spins. The RF signal is transmitted in the Carr-Purcell sequence by the digital pulse generator.

The LNA in Fig. 7.3.3 is critical for receiver sensitivity. Its schematic is in Fig. 7.3.4. At 21.3MHz, the overall LNA noise is dominated by the channel thermal noise of the input transistors, which is decreased by increasing tail current to 4mA and gate width to 900 $\mu$ m. The cascode structure of the LNA mitigates the feedthrough of the local oscillator signal to the LNA input, which can mask the true NMR signal. At 21.3MHz, the LNA's voltage gain is 110, and its input referred noise should be below 2.5nV/ $\sqrt{Hz}$ , the measured input referred noise of the whole receiver. To handle the wide range of the NMR signal power, a VGA follows the LNA. The IC was fabricated in 0.18 $\mu$ m CMOS (Fig. 7.3.1).

Figure 7.3.5, top, shows the measured, down-converted NMR signal of 5 $\mu$ L water held on the planar microcoil. The signal is a sequence of attenuated spin echoes.  $T_2$  of 523ms is extracted from the exponentially decaying envelope (dotted line) of the spin echoes. The repeated spikes are a coupling of the transmitted RF sequence into the receiver. As magnetic nanoparticles (~30nm) are put into the water, they introduce spatial and temporal magnetic field modulations on top of  $B_0$ , which intensifies loss of phase coherence in spin precessions, decreasing  $T_2$ . With magnetic nanoparticles (0.17mM) in water,  $T_2$  reduces to 60ms (Fig. 7.3.5, bottom). The measured  $T_2$  with various densities matches the theory.

While the planar microcoil ( $Q=16$ ,  $L=500$ nH) used to obtain Fig. 7.3.5 was ultimately part of our system due to its microfabrication advantage, a similar experiment was performed using a higher- $Q$  solenoid microcoil ( $Q=200$ ,  $L=300$ nH) to show the spin echoes more clearly; with higher- $Q$ , spin echoes are much stronger than the spikes (Fig. 7.3.6). As the magnetic particle concentration changes from 0.1mM to 1mM,  $T_2$  is reduced from 150ms to 15ms (Fig. 7.3.6).

The relaxometry capability of the CMOS NMR system can be used to sense biomolecules. Consider, for example, magnetic nanoparticles with surfaces coated with biotin (vitamin) that specifically bind to avidin (protein). If avidin exists in a sample, the coated magnetic particles suspended in the sample self-assemble into clusters [2] (Fig. 7.3.7). The clustering (hence avidin) can be sensed, for the clusters introduce greater spatial and temporal magnetic field modulations, reducing  $T_2$ . This detection scheme, called magnetic relaxation switch [2], is a general sensing modality that can detect a variety of target biomolecules (e.g., proteins, cancer markers [2]).

Figure 7.3.7 shows  $T_2$  reduction in the presence of avidin (320nM) due to the magnetic relaxation switch, measured with the system of Fig. 7.3.1. The measured detection threshold of the system is 20fmol avidin (in ~5 $\mu$ L, *i.e.*, 4nM), which is 60× more sensitive than the commercial, state-of-the-art benchtop NMR relaxometer [1]. The sensitivity and size bode well for the CMOS NMR system as a portable, low-cost general and diagnostic NMR relaxometer.

#### References:

- [1] "Minispec". Accessed on Nov. 19, 2007, <<http://www.theminispec.com/>>.
- [2] J. M. Perez, et al., "Magnetic Relaxation Switches Capable of Sensing Molecular Interactions," *Nature Biotechnology*, vol. 20, pp. 816-820, Aug. 2002.
- [3] H. Lee, E. Sun, D. Ham, and R. Weissleder, "Chip-NMR Biosensor for Detection and Molecular Analysis of Cells," submitted for review, 2007.
- [4] G. Boero, et al., "Fully Integrated Probe for Proton Nuclear Magnetic Resonance Magnetometry," *Rev. Sci. Instr.*, vol. 72, pp. 2764-2768, June 2001.
- [5] T. Cheriñ, et al., "A CMOS Microcoil-Associated Preamplifier for NMR Spectroscopy," *IEEE Trans. Circ. Sys. I*, vol. 52, pp. 2576-2583, Dec. 2005.
- [6] L. Fan, et al., "Miniaturization of Magnetic Resonance Microsystem for 3D Cell Imaging," *ISSCC Dig. Tech. Papers*, pp. 166-167, Feb. 2007.
- [7] J. Perlo, et al., "High-Resolution NMR Spectroscopy with a Portable Single-Sided Sensor," *Science*, p. 1279, May 2005.

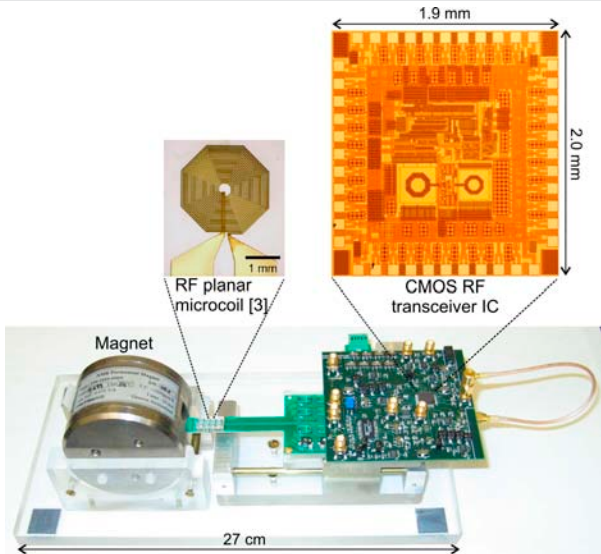


Figure 7.3.1: The CMOS mini-NMR system.

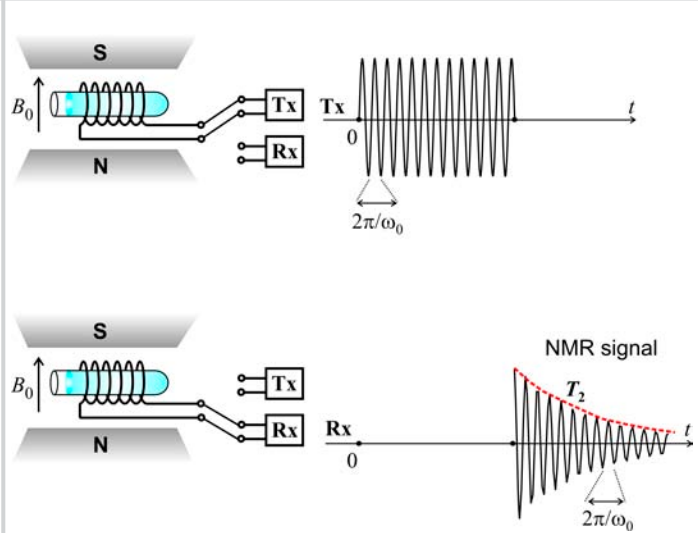


Figure 7.3.2: Basic NMR operation.

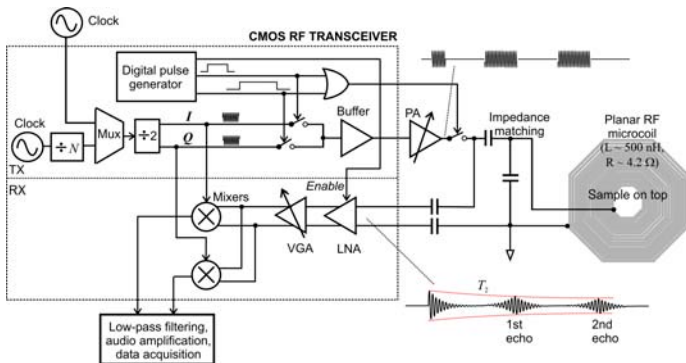


Figure 7.3.3: CMOS RF transceiver architecture used in the mini-NMR system.

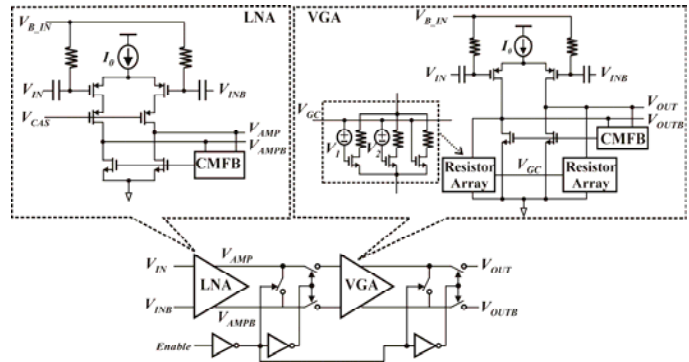


Figure 7.3.4: LNA and VGA.

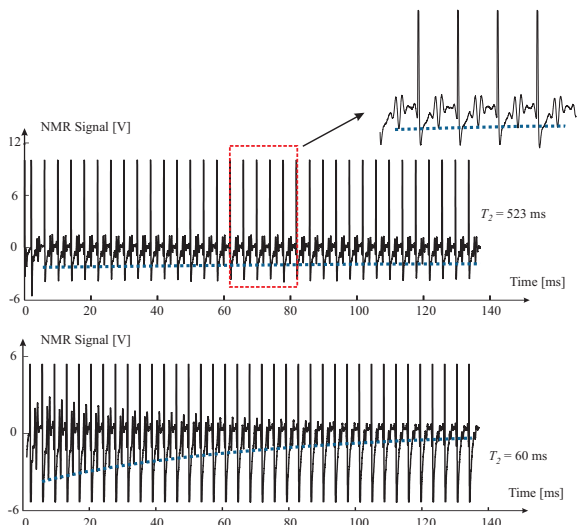


Figure 7.3.5: Measured NMR signals with the planar microcoil: (top) pure water, (bottom) water with magnetic particles.

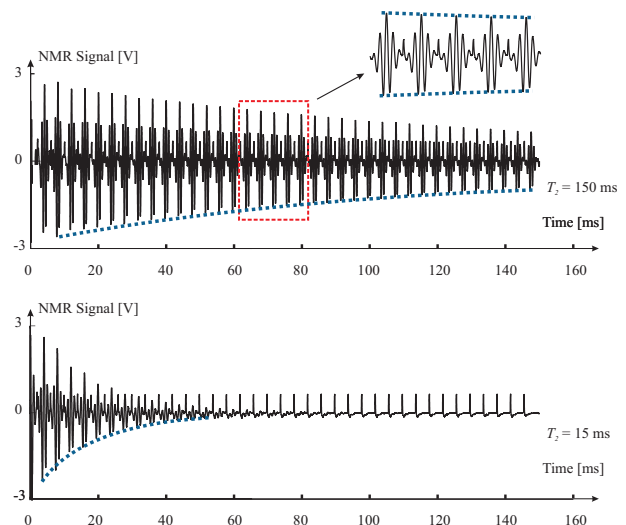


Figure 7.3.6: Measured NMR signals with a solenoidal microcoil with two different concentrations of magnetic particles.

Continued on Page 602

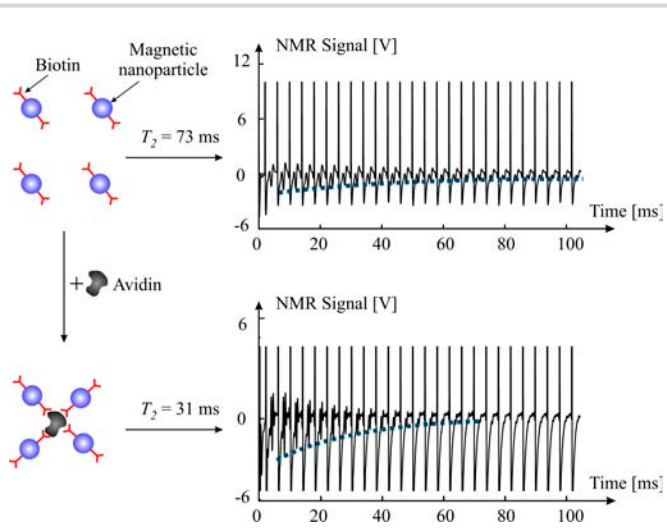


Figure 7.3.7: Experimental avidin detection using the CMOS mini-NMR system.