Palm NMR and One-Chip NMR

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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. 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 60× lighter, 40× smaller, yet 60× 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 order-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 20× lighter, 30× smaller, yet 25× 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 1200× lighter, 1200× smaller, and yet 150× more spin-mass sensitive. Production cost reduction is 1400×. To achieve this further order-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 (~10^4) 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 on-chip coil. As the signal is already weak owing to the small magnet, we designed a partially integrated, high-performance RF transceiver and a separate coil.

The integrated transceiver (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 \(\omega_0\), amplitude \(\omega_{0\text{exc}}\)). For a given duty cycle, the square wave has a particular power distribution of harmonics. The harmonic distribution varies with duty cycle. Only the \(\omega_0\) component matters, since higher harmonics lie outside the ‘proton filter’ band: protons are a high-Q (~10^4) filter centered at \(\omega_0\), as they are not excited outside the band. As duty cycle changes from 0 to 50%, the \(\omega_0\) component changes from 0 to 0.63\(\omega_{0\text{exc}}\). This leads to output power tuning. The input to the duty-cycle controller (Fig. 27.2.4) is a square wave (\(\omega_0, \omega_{0\text{exc}}\)) 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 \(\omega_0/\omega_{0\text{exc}}\), 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 \(V_{\text{Inv}}\). Inv-2, a complementary current-starved inverter, prevents the steady delay increase for small \(V_{\text{Inv}}\). Inv-3, a current-starved inverter with a source follower, sustains a delay reduction with increasing \(V_i\). 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 LNAs 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 cascode-mode feedback; as resistive loads produce lower gain, a passive 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 \(\omega_0\). 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), \(T_2\)=100ms from their decay envelope. Magnetic particles (38nm) coated with biotin 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 2.5× higher than our prior work [1,2], and 150× 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. \(T_2\)=169ms 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 60× higher than the commercial system.

References:
Figure 27.2.1: Palm NMR system.

- 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 27.2.2: One-chip NMR system.

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

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.