28.1 A Handheld 50pM-Sensitivity Micro-NMR CMOS Platform with B-Field Stabilization for Multi-Type Biological/Chemical Assays

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Point-of-use (PoU) biological/chemical assays are aimed to transform bulky laboratory instruments into easy-to-use lab-on-a-chip platforms, bringing down the cost, size, and sample-use by orders of magnitude [1,2]. Micro-Nuclear Magnetic Resonance (NMR) is a trail-blazing tool for *target* pinpointing, by utilizing functionalized magnetic nanoparticles (MNPs) as the *probe* [3]. Screening by micro-NMR is repeatable, versatile and low-cost as it is label- and washing-free for the samples, and immobilization-free for the electrodes. Herein, a high-sensitivity micro-NMR CMOS platform with magnetic (B)-field stabilization and thermal management is reported (Fig. 28.1.1). This handheld tool unifies multi-type assays (target detection, protein state analysis, and solvent-polymer dynamics), and is suitable for healthcare, food industry, and colloidal applications.

Micro-NMR relaxometry detects the spin-spin relaxation time (T_2) by extracting the echoes envelopes from the response of the non-zero spin nuclei (i.e., ^{1}H). The nuclei, under magnetization with a static magnetic field (B_0), absorb orthogonal RF exciting magnetic field (B_1) at the Larmor frequency, $f_L=\gamma B_0$ (γ: gyromagnetic ratio), and precess about the direction of magnetization at f_L even after the cessation of the excitation. In an existing micro-NMR system [3], frequency deviation of the local oscillator (LO) from f_L induces improper frequency excitation, paralyzing the operation. Confounded by the thermal instability of the portable magnet (B_0=0.46T, T.C.=-1200ppm/K), LO tracking is essential to safeguard the system against environmental changes.

Our micro-NMR platform (Fig. 28.1.2) is tailored with B_0-field stabilization and thermal management to enhance the robustness and simplify the hardware. The dynamic B_1-field transduction is based on a spiral coil driven by a transmitter (TX)/receiver (RX) together with a matching capacitor C_M, to excite/obtain the magnetic signal to/from the droplet samples (2.5μL) normal to the chip surface. The TX is based on a tapped inverter-chain power amplifier (PA), measured 31.6% power efficiency, to deliver programmable pulse sequences pertaining to the LO. The RX features a multi-stage low-noise amplifier (LNA) for high RX sensitivity (down to 1nV/√Hz input-referred-noise), and a dynamic-bandwidth lowpass filter for fast recovery from saturation after excitation pulses. The B_0-field sensor and calibrator manage the lateral B_0-field together with a current driver, which injects a calibration current to the magnet (75mT/A) stabilizing the bulk magnetization on the nuclei. The spiral coil also serves as a heater allowing thermal profiling of the samples. The thermal-induced error on the B_0-field sensor and calibrator, and the hotness of the samples, are monitored by a BJT temperature sensor.

To sense the lateral B_0-field normal to the chip surface, a *current-mode* 4-folded vertical hall sensor (VHS) arranged in a Wheatstone bridge is employed (Fig. 28.1.3). Each VHS element is composed by an n-well as the substrate and three n-diffusions as contacts [4]. P-diffusions are embedded between the n-diffusions to avert current flowing at the surface, soothing the *1/f* noise. To achieve sub-nA sensitivity, the VHS readout circuit (Fig. 28.1.3) is based on a low-noise TIA. Current-spinning and chopper are applied reducing the *1/f* noise corner by >5,000×. Switches $S_{1\text{-}8}$ control the flows of the current and reset the capacitors C_F. Small switches (280Ω each) can exacerbate the impedance of the TIA, ($R_{in,TIA}$=210Ω) if there is current passing through the switches connected between the core OTA of the TIA and VHS (i.e., $S_{5\text{-}6}$). To address this, $S_{7\text{-}8}$ are managed to guide the current passing through the negative feedback path, nullifying the impact of resistances of $S_{5\text{-}6}$ on the TIA. Thanks to this switching scheme, $R_{in,TIA}$ is suppressed by 84%, absorbing ~21% more current into the TIA than the general approach [5].

Attributed to the prodigious nominal B_0-field, a typical TIA can be saturated and fail to sense the tiny B_0-field variation (3.75mT). To solve it, a nominal B_0-field compensator made by a passive switched-capacitor network (Fig. 28.1.3) nullifies the nominal B_0-field entering into the TIA.

Before the micro-NMR assay, the VHS reads B_0 and responds to the current driver (Fig. 28.1.4). B_0 may shift away from its nominal value due to the environmental changes (e.g., temperature and sample-to-magnet position). Thus, untracked f_L can be easily off-center from the LO frequency f_{OSC} (BW=16.7kHz), Here, by modulating the magnet according to an updated B_0 (sensitivity: 4.12V/T), f_L is reset to f_{OSC}. Also, with signal-averaging performed in the frequency domain to suppress the background noise, the calibration improves the B_0-field stability by 13× (from 2 to 0.15mT) at 0.46T (f_L=19.6MHz). Under the synergy of micro-NMR and VHS, the stabilized f_L inspires the use of a simple crystal oscillator as the LO that measures low phase noise (-116dBc/Hz at 1kHz offset) at very low power (79μW).

Human Immunoglobulin G (IgG), which protects the body from infections, can be quantified by utilizing Protein A coated water-soluble MNPs (i.e., Fe_2O_3) based on their T_2. T_2 of the sample is shortened commensurate with the amount of IgG upon nanoparticles agglomeration, enabling quantification of IgG down to 5nM (Fig. 28.1.5). The specificity of micro-NMR assay is evinced with the addition of Chicken Immunoglobulin Y (IgY), which does not conjugate with Protein A. The negligible change of T_2 (<2%) validates the selectivity of the assay. The versatility of the platform is manifested with DNA detection apt for life-threatening bacteria screening. With a pair of probe-decorated MNPs, the platform quantifies the synthesized DNA derived from *Enterococcus faecalis*, with a detection limit down to 50pM in 2.5μL samples (125amol). By varying the MNP concentration, the detection range is impelled to 125nM. The response to single-nucleotide polymorphism is indistinguishable to T_2 baseline (<4%), substantiating that single-base mismatch DNA can be differentiated.

Probing the molecular structure can digest the protein state for food quality inspection. Protein β-lactoglobulin (β-LG) denatures and aggregates irreversibly after heating to >60°C [6]. This state transformation can be embodied by measuring T_2 of the samples attributed to the dissimilar interaction between the water molecules and protein at different states and sizes (Fig. 28.1.6). For the colloidal industry, Poly(N-isopropylacrylamide) (PNIPAM) is widely used as advanced sensor and drug delivery carrier [7]. It is a colloidal polymer that exhibits a temperature-induced reversible volume phase transition in water, affects the local environment on solvent confinement and thus T_2 of the solvent. By duty-cycling the heater (coil), PNIPAM undergoes a volume phase transition above 33°C, resulting in T_2 decrement of the solvent.

Benchmarking with the recent PoU tools (Fig. 28.1.7), this work supports multi-type assays in one unified platform, while achieving high sensitivity and selectivity for DNA, as well as other proteins targeting capability in tiny sample with functionalized MNPs. The platform consumes 120× less samples, and is 96× lighter, 175× smaller, and 16× cheaper than a commercial product (Bruker mq-20 [8]).

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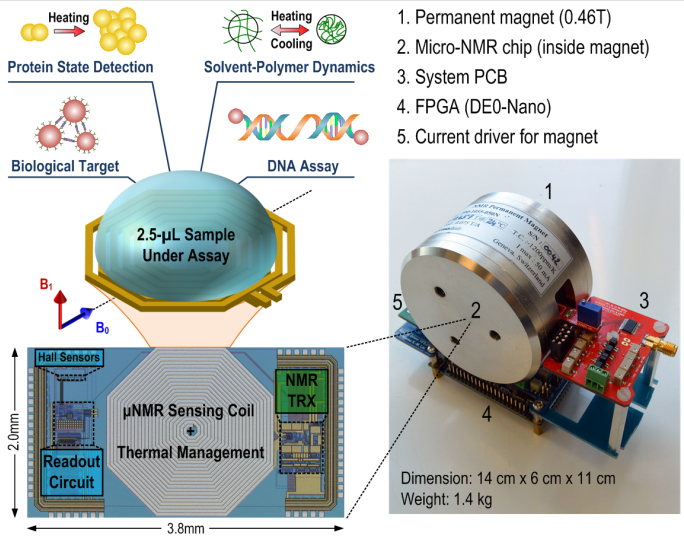

Figure 28.1.1: A micro-NMR CMOS platform with B-field stabilization: (left) chip photo and (right) platform assembly.

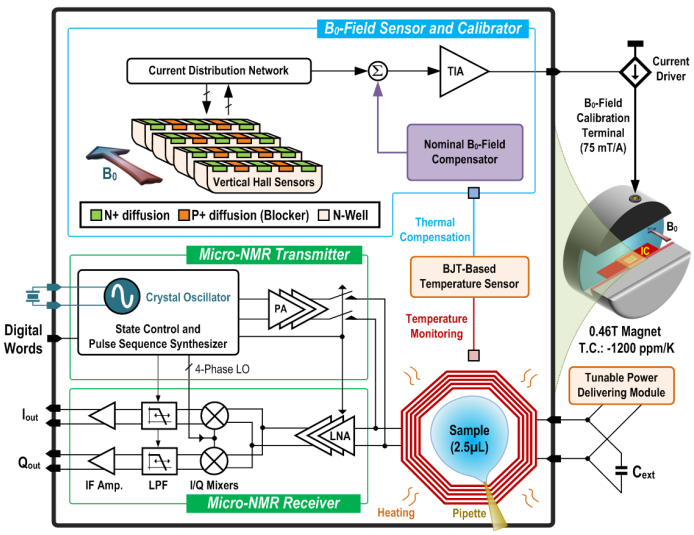

Figure 28.1.2: System block diagram.

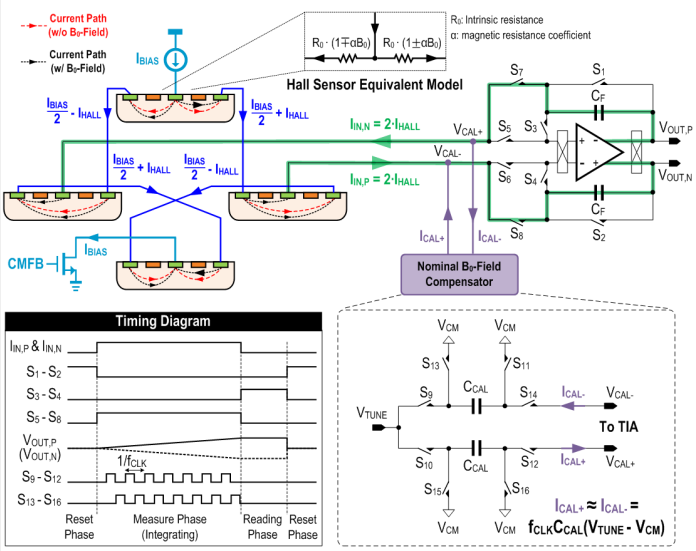

Figure 28.1.3: Current-mode 4-folded VHS to sense the lateral B_0-field.

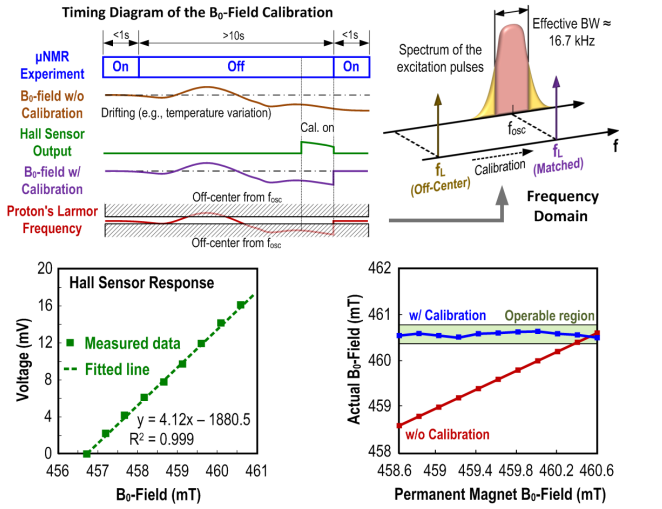

Figure 28.1.4: (Top) Timing diagram of the B_0-field calibration and its frequency domain illustration. (Bottom) Measured Hall sensor response and B_0-field with and without calibration.

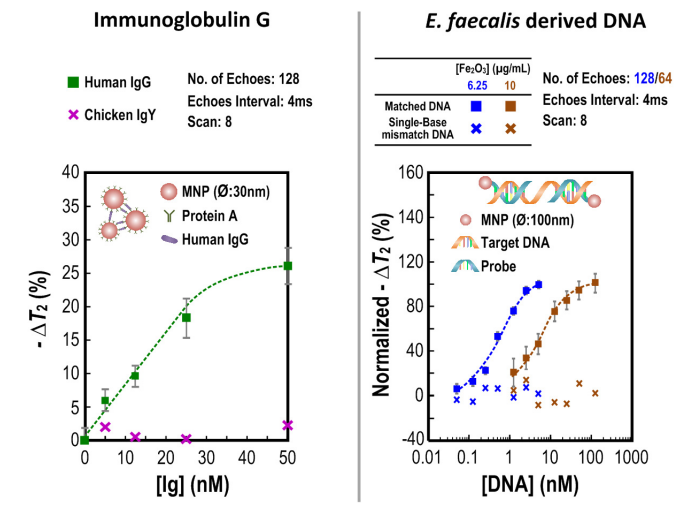

Figure 28.1.5: Examples of target detection: (left) from Human IgG as target, and Chicken IgY as control; (right) from E. faecalis derived DNA and single-base mismatch DNA.

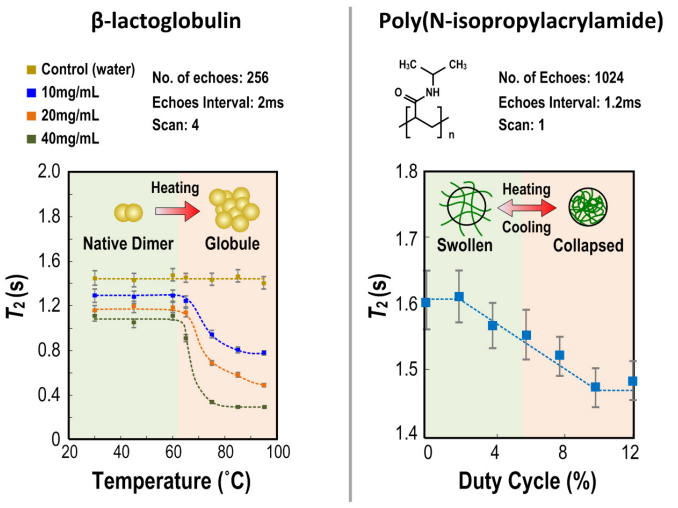

Figure 28.1.6: Examples of state analysis reflected by T_2: (left) thermal profiling of protein (β-LG) state; (right) polymer (PNIPAM) dynamics during heating and cooling.

		This Work	P.-H. Kuo *et al.*, ISSCC'15	K.-H. Lee *et al.*, ISSCC'12	N. Sun *et al.*, ISSCC'10	B. Jang *et al.*, ISSCC'09
Application	Specificity	**1. Target detection 2. Solvent-Polymer dynamics 3. Protein state analysis**	Target detection	Target detection	Target detection	Target detection
	Target Labeling	**Label-free**	Label-free	Label-free	Label-free	Cy3-label
	Demo Target	**68 base *E. faecalis* derived DNA**	NT-ProBNP & TNF-alpha	21 base H5N1 virus	hCG cancer marker	18 base DNA
	Detection Limit	**50 pM (DNA)**	--	100 pM (DNA)	5000 pM (Cancer marker)	125 pM (DNA)
	Sample Handling Limit	**2.5 µL**	--	--	5.0 µL	--
Hardware	Physics	**NMR relaxometry + Thermal management**	Magnetic-sensing	Capacitance-sensing	NMR relaxometry	Fluorescent-sensing
	Post-Fabrication Necessity	**No (immobilization free)**	Probe (antibody) immobilization	Probe (DNA) immobilization on Au electrodes	No (immobilization free)	Fiber-optical faceplate
	External Part	**Portable magnet**	No	No	Portable magnet	Light source
	LO Generation	**Crystal oscillator + B_0-field calibration**	--	--	Off-chip	--
	Robustness to environments	**Robust to temperature & sample position variations**	Robust to temperature variation	Vulnerable to bias current variation	Vulnerable to B-field variation	Vulnerable to background noise
	CMOS Tech.	**0.18 µm**	0.35 µm	0.35 µm	0.18 µm	0.35 µm
	Chip Area	**7.6 mm²**	8.9 mm²	20.0 mm²	11.3 mm²	9.0 mm²

Figure 28.1.7: Benchmark with other CMOS-based PoU systems.

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