A THERMAL-INSENSITIVE ALL-ELECTRONIC MODULAR µNMR RELAXOMETER WITH A 2D DIGITAL MICROFLUIDIC CHIP FOR SAMPLE MANAGEMENT

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ABSTRACT

Presented is an electronic-automated micro-Nuclear Magnetic Resonance (µNMR) relaxometer with multi-sample droplet management capability for Point-of-Care diagnostics. Constraints of sample handling inside the cramped magnet are overcome by integration of microfluidic and microelectronic technologies. The two-dimensional digital microfluidic (DMF) device with sample location detecting capability enables automatic sample manipulation. Additionally, a calibrator ensures precise proton excitation against ambient temperature (18-30°C). Experiments have corroborated auto-handling and identification of two targets within 2.2 minutes, indicating it as a promising tool for Point-of-Care application.

KEYWORDS: Nuclear Magnetic Resonance, Biosensor, Digital Microfluidic.

INTRODUCTION

Point-of-Care (POC) diagnostics plays critical roles in healthcare system, especially for developing world and remote area where stable power sources and standard laboratory equipment are limited. Additionally, these POC diagnostics platforms should be free from sample preparation and capable of sensing multiple targets simultaneously to diminish the experiment time and optimize the efficiency of the diagnosis [1]. Herein a modular µNMR relaxometer for POC diagnostics is reported (Fig. 1a). Affected by the magnetic properties of the samples, the spin-spin relaxation time (T_2) from the samples correlates with the concentration of the targets inside the samples thus the quantity of the analyte can be identified. The µNMR relaxometer equips with a complementary metal oxide semiconductor (CMOS) transceiver to perform NMR assays on the samples via a Butterfly-Coil. To reduce the chance of sample defilement, a two-dimensional DMF device (Fig. 1b) is integrated for electronic-automated sample manipulation. Associated with the capacitive sensing module, the positions of the samples inside the DMF device are detected by the relaxometer, culminating in a fully-automated and optimum sample management scheme. To circumvent the magnetic field variation of the portable NdFeB magnet (0.458 T, 1.2 kg) caused by the ambient temperature shift, a calibrator is included to sense the temperature and drive the auxiliary coil of the magnet to compensate the magnetic field variation.

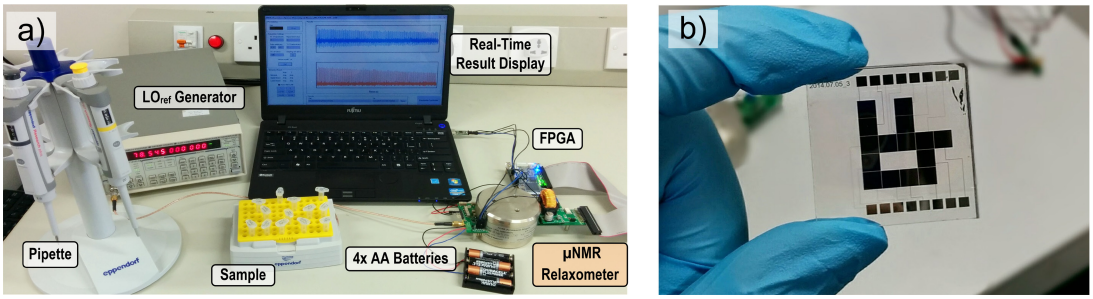

Figure 1: (a) Proposed µNMR relaxometer. The entire relaxometer including droplets path optimization is mastered by the PC, easing the operation of the relaxometer and befitting for POC diagnostics. (b) The top plate of the two-dimensional DMF device, which is coated with 15 Chromium Electrodes.

THEORY

The modular µNMR relaxometer includes a Butterfly-coil-input CMOS transceiver (1.6mm x 1.3mm). Enables by the advance in microelectronic technology [2,3], the transmitter emits the Carr-Purcell-Meiboom-Gill spin-echo pulses and drives up the Butterfly-coil by a power amplifier whereas the receiv-

er, with simulated input-referred noise of 920pV/√Hz, amplifies the NMR signals from the coil to perform high sensitivity NMR assays, which is unattainable with the discrete prototype [4]. The PCB fabricated Butterfly-coil (60.0mm^2) can transduce between magnetic and electrical signals inside the space limiting magnet by generating a plane-parallel magnetic field.

As the magnetic field of the portable magnet is temperature dependent (T.C. -1000ppm/K), the Larmor frequency of the protons shift accordingly which lead to malfunction of the relaxometer. Hence a calibrator is included to sense the temperature and drive the auxiliary coil of the magnet to compensate the field variation thus a fix excitation frequency can be adopted to simplify the electronic systems, enhancing the robustness of the relaxometer for application at different environments.

The DMF device equips with a capacitance-to-digital module to coordinate multiple ~10μL droplets in real time. It includes two parallel glass plates fit-in the 32mm inner width of the magnet, where the top plate is coated with Chromium electrodes and multi-layer dielectric materials. The bottom plate is the ground coated with Indium Tin Oxide (ITO). Both plates were finished with hydrophobic Teflon layers to enlarge the contact angle variation (i.e., lower driving voltage). Additionally, the capacitance-to-digital module scans the location of the droplets by detecting the capacitance of the electrodes.

EXPERIMENTAL

Two analytes detection [Copper (II) Sulfate and avidin] were demonstrated. Different concentration of $CuSO_4$ samples were prepared from Copper (II) sulfate pentahydrate from Aladdin® (Industry, CA). For the detection of avidin, biotinylated Iron nanoparticles (Φ: 30nm) from Nanocs Inc. (New York, NY) were entailed as probe to bind with the avidin. Different concentrations of avidin were prepared from avidin powder which were purchased from Sigma-Aldrich Co. (St. Louis, MO).

For the hardware, the CMOS transceiver was fabricated with GlobalFoundries Inc. (Santa Clara, CA) in 0.18μm process with 1 polysilicon and 6 metal layers. The Butterfly-Coil was fabricated on PCB with conductor width and spacing of 6 mil. The overall system is mastered by the laptop via USB-interfaced field programmable gate array (FPGA) DE0-Nano from Terasic Inc. (Taiwan). The portable magnet was purchased from Metrolab Technology SA (Switzerland).

RESULTS AND DISCUSSION

The static magnetic field of the magnet was measured from 18°C to 30°C by varying the temperature inside the temperature chamber. Without the magnetic field calibrator, the magnetic field decreases linearly from 18°C to 30°C with variation of 5.54mT, corresponding to Larmor frequency shift of 235.9kHz. With the magnetic field calibrator (Fig. 2a), the current driver can compensate the magnetic field change attributed to the temperature variation by injecting a corresponding current to magnet. The magnetic field variation is suppressed to 0.07mT (i.e., 3kHz) with calibration (Fig. 2b).

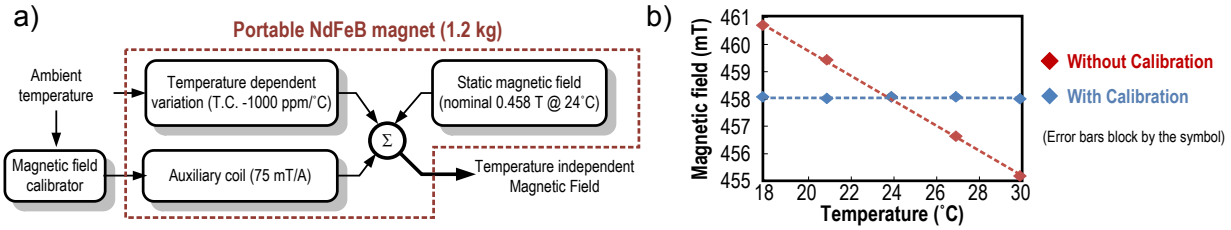

Figure 2: (a) Schematic of the magnetic field calibrator. (b) Measured magnetic field (from 5 measurements).

The functionality of the μNMR relaxometer was demonstrated by chemical ($CuSO_4$) and biological (avidin) samples. The μNMR can detect the $CuSO_4$ concentration with T_2^{-1} increases linearly attributed to the magnetic moments of Cu^{2+} ions (Δ: 1.05s^{-1}mM^{-1}, R^2:0.998). The μNMR relaxometer can also detect unprocessed biological targets with a pre-designed probe. Bound to the avidin in the sample, the biotinylated magnetic nanoparticles form micro-clusters and thus the T_2 of the samples decrease linearly with the concentration of avidin (Δ: -45.5s·mM^{-1}, R^2:0.993).

To demonstrate the multi-sample management capability of the relaxometer, protocol for pinpointing multiple avidin targets was demonstrated (Fig. 3a). By applying signal on the designated electrodes, the relaxometer, which manages the time schedules and interference-free routes of both droplets, can transport the droplets to the µNMR sensing site (Fig. 3b). The concentration of the target can be pinpointed by their T_2 respectively. This 2.2-minute experiment validates the entire system as being capable to reduce the labor work/error and risks of defilement, rendering it a suitable tool to replace benchtop laboratory apparatus for POC diagnosis applications.

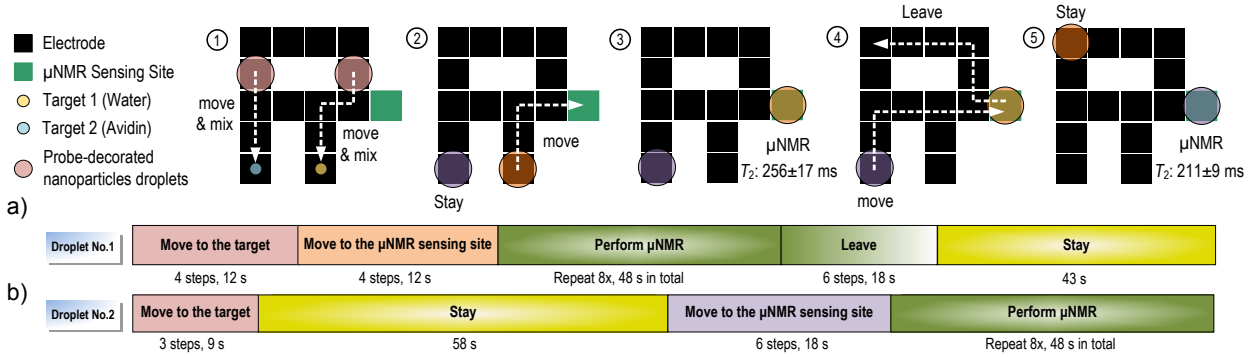

Figure 3: (a) Illustrations of the motions of multi-step multi-sample µNMR assays. Two probes are placed inside the DMF device together with two targets. Their concentration can be pinpointed by their T_2. (b) Gantt chart of operation for the droplets. The routes of the droplets and the protocols can be optimized at software level.

CONCLUSION

µNMR relaxometer for POC diagnostics with electronic-automated sample management scheme was reported in the paper. A CMOS transceiver is equipped to perform high sensitivity µNMR assay and a DMF device with capacitance-to-digital module forms a closed-loop control and regulates the route and position of the droplets automatically. A calibrator is integrated with the µNMR relaxometer and the field variation of the magnet is suppressed, rendering it suitable for application at different environment. Experimental results showed the capability of the µNMR relaxometer to detect unprocessed chemical ($CuSO_4$) and biological (avidin) samples. Additionally, diagnosis of different samples inside the µNMR relaxometer with automated sample management was demonstrated within 2.2 minutes, hence reducing human efforts and chance of sample contamination while optimizing the assay efficiency.

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