Highly Integrated, Low Cost, Palm-Top Sized Magnetic Resonance Relaxometry System for Rapid Blood Screening

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Abstract— **A highly integrated, palm-top sized radio-frequency Magnetic Resonance Relaxometry System (19cm x 16cm x 5cm, weigh 250g) is developed. In this work, we show strategy on how to integrate all the modules into a single mother board which consists of coin-sized permanent magnet, miniaturized radio-frequency microcoil probe, compact lumped-circuit duplexer, and single board 4-Watt power amplifier, in which a FPGA-based spectrometer is used for pulse excitation, signal acquisition and data processing. We demonstrated that by measuring the proton transverse relaxation rates from a large pool of natural abundance proton-nuclei presence in less than 1 µL of red blood cells, one can indirectly deduce the relative magnetic susceptibility of the bulk cells within a few minutes of signal acquisition time.**

Keywords— **Magnetic Resonance Relaxometry, FPGA, NIOS-II based architecture, CORDIC.**

I. Introduction

With advances in microelectronics technology, Magnetic Resonance (MR) community sees the emergence of much more compact MR spectrometers [1-4] on a highly integrated circuit platform such as field programmable gate array (FPGA), and complementary-metal oxide semiconductor (CMOS). Here, in Singapore-Massachusetts Institute of Technology for Research and Technology (SMART Centre), a novel, compact-sized, and portable (250g) Magnetic Resonance Relaxometry (MRR) system is designed and developed [1-2]. The whole system consists of a coin-sized permanent magnet (0.76 Tesla), miniaturized radio-frequency microcoil probe, compact lumped-circuit duplexer, and single board 4-Watt power amplifier, in which a FPGA-based spectrometer is used for pulse excitation, signal acquisition and data processing.

We show that by measuring the proton transverse relaxation rates from a large pool of natural abundance proton-nuclei presence in less than 1 µL of red blood cells (RBCs), one can indirectly deduce the relative magnetic susceptibility of the bulk cells within a few minutes of signal acquisition time [1, 5-6]. Such rapid and sensitive blood screening system can be used to monitor the fluctuation of the bulk magnetic susceptibility of the biological cells (e.g. human red blood cells), where unusual state of the bulk magnetic susceptibility is related to a number of diseases (e.g. malaria, sepsis, methemoglobinemia, genetic diseases, etc).

II. System Design and Implementation

A. Single, Compact Mother Board Design

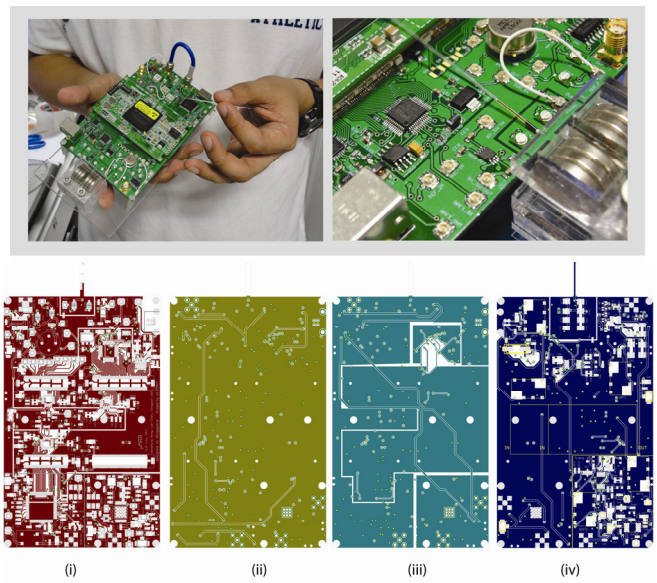

Fig. 1: (Top) Snapshot of the developed palm-top MRR system. (Bottom) Circuitry layout of the system: (i) Top Component Layer, (ii) Second Layer (Digital Power Plane), (iii) Third Layer (Analog-Ground Plane), and (iv) Bottom Component Layer.

The entire system consists of a single, palm-sized (19cm x 16cm x 5cm) 4-layers printed circuit board which hosts the core functionality for MMR system: transmitter, power amplifier, pre-amplifier, miniaturized passive duplexer and rf-probe (Fig. 1). The rf-transmission and receiving mode is controlled by a centralized FPGA [3-4]. The main architecture of this work is based on previous published [1-2]. A 4

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turns hand-woven microcoil rf-probe (<1µL volume, i.d:550µm) is integrated directly into the base-board, with its ground separated from the rest of the board to avoid coupling noises. In this current work, a new and much more powerful power amplifier than previously published works [1-2] were also being introduced. A cascaded of three broadband Monolithic Microwave Integrated Circuit (MMIC) devices, (i) two cascaded power amplifiers, and (ii) one rf-switch were integrated to produced an maximum output of 4 Watts (Fig. 2). The first stage is to deliver a high gain (usually much lower power), while the second stage is to produce a much higher output power (despite a low gain) (Fig. 2a). In the first booster stage, GALI-74+ (Mini-Circuits, USA) is used to give a high gain of 25dB. The second MMIC amplifier (AM003536WM, AMCOM USA) produces an eventual 36dBm output power (23dB gain). A combination of these two cascaded stages is able to amplify, -12dBm input signal to 36dBm (or 4 Watts), which translates into an overall gain of 48dB (at 100MHz). A 5-Watt, fast switching (~100ns) RF-switch (HMC574MS8, Hittite Microwave) is employed to block out the noise leakage during the NMR signal acquisition period. A high-speed CMOS Logic Hex Inverter (CD74HCT04, Texas Instruments) is used to convert the input gating/unblank signal into two complimentary control signals required by this SPDT-switch.

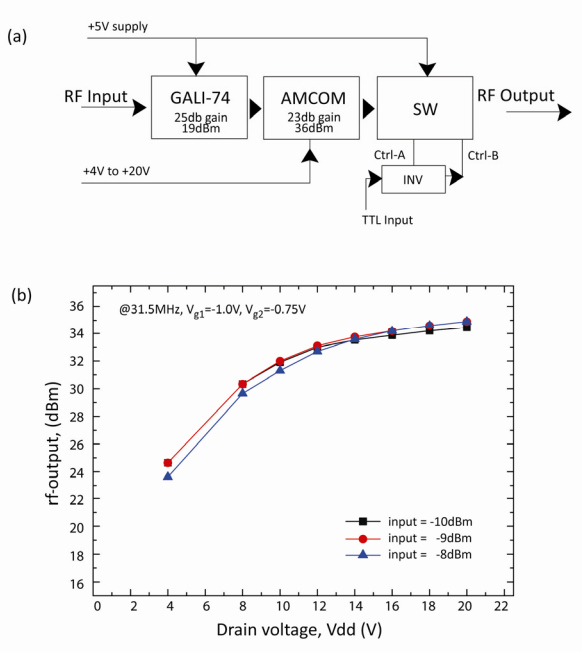

Fig. 2: (a) Schematic diagram of the 2-stages power amplifier with the maximum output of 36dBm developed in this work. The acronym were SW=Switch and INV=Inverter. (b) RF-output as a function of various supply voltages, V_{dd} at signal input of -10dBm, -9dBm, and -8dBm.

B. Future Direction: Stand-alone System with Nios-II Soft Processor

In order to develop a standalone system where host PC is not available, NIOS II soft processor can be introduced. One can exploit the soft-architecture system-on-a-programmable-chip (SOPC) builder, provided by Quartus II. The host computer interface is implemented through Nios-II UART and connected to a FT232R chip. This interface is much faster and user-friendlier as compared to the EIA-232 protocol [3- 4]. Nios II enables simpler connectivity of the FPGA to other peripheral devices, like Serial Peripheral Interface (SPI) OLED display screen (Fig. 3).

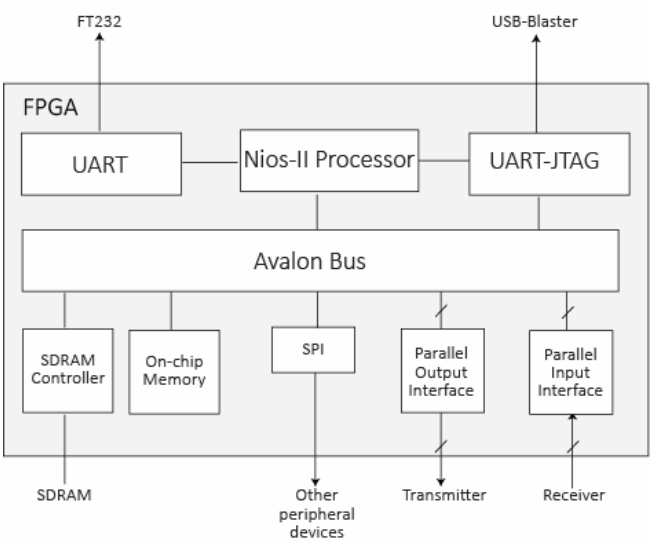

Fig. 3: Design Flow Chart for Nios-based FPGA module. 144-pin Altera Cyclone III chips (EP3C25E144C8N), which operate as transmitters and receivers, were used to replace the 780-pin chip of Altera Cyclone III (EP3C80F780C8N) [1-3]. We overcame the trade-off of low cost and low memory resource FPGA by optimizing VHDL code and using other auxiliary circuitry and on-board SDRAM. The old EIA-232C protocol is replaced by NIOS II serial communication to improve the communication between hardware and software [3-4].

One can also further utilize the parallelism of the FPGA by implementing a Quadrature Amplitude Modulator (QAM) based on Coordinate Rotation Digital Computer (CORDIC) architecture (Fig. 4). This design exploits the interconnected adders/subtracters constructed by VLSI inside the FPGA to replace physical on-board multipliers and ROM-costly sine/cosine look-up tables [7]. CORDIC uses simple shift-add operations, to perform several computing tasks such as the calculation of trigonometric, hyperbolic and logarithmic functions, real and complex multiplications.

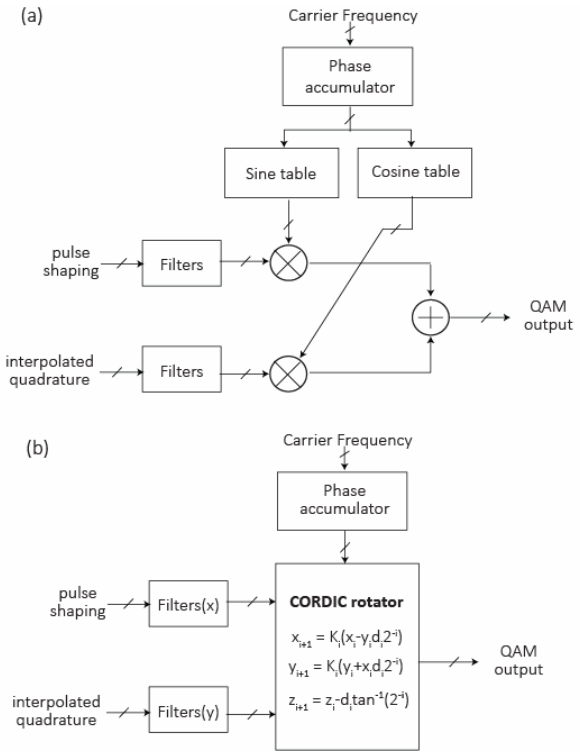

Fig.4: QAM modulator architecture. (a) The QAM modulator requires on-board multipliers and adders in conventional architecture. A much larger ROM is needed to store the discrete values sine-cosine generated from the look-up table. (b) With CORDIC rotator, the multipliers and adders are replaced by the internal adders/subtracters unit of FPGA. Furthermore, sine/cosine generators are implemented through a series of approximations. K_i is CORDIC coefficient; d_i is the control variable: d_i=-1 if $z_i < 0$ and +1 otherwise. The accuracy of results will be increased by 1 bit after each step of iteration, because CORDIC is a bit-recursive algorithm [7].

III. MRR SYSTEM DEMONSTRATION

A. Rapid and highly sensitive blood screening system

Met-Hb (ferric state, Fe (III)) is prepared in *in-vitro* environment by mixing sodium nitrite in excess to freshly prepared blood, which is predominantly in the oxygenated state. The 'redox-titration' curve (Fig. 5) reveals that both T_1 and T_2 relaxations dropped drastically (steep-zone in Fig. 4) in response to high nitrite concentration (>100 µM) due to the drastic switching of MR states. This simple oxidation however, trigger a drastic transformation of magnetic state from much lower diamagnetic states (with no unpaired electron) to the highly paramagnetic state due to the presence of 5-unpaired electron in met-Hb. It reached a plateau state in high concentration zone (>6 mM) with full conversion of met-Hb has MR state with coordinate (T_2=108ms, T_1=185ms), while its' original fully oxygenated–hemoglobin has MR states of (T_2=182 ms, T_1= 698 ms).

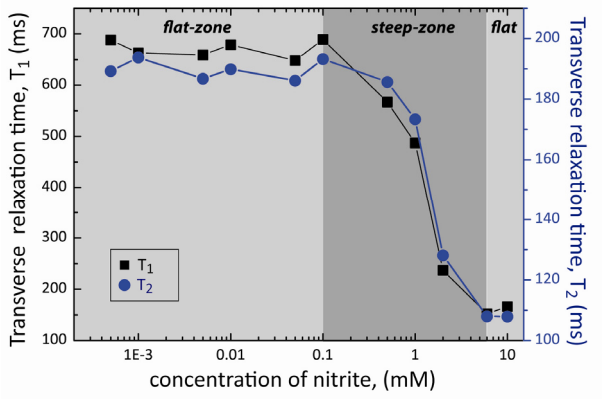

Fig.5: Ferric, Fe (III) formation: Nitrite concentration profile in T_1 and T_2 relaxation times of packed RBCs as function of various nitrite concentrations over for 30 minutes of exposure to oxy-hemoglobin, Fe(II) obtained from consented healthy donor. ^{1}H MRR measurements of bulk red blood cells at the resonance frequency of 32.4 MHz inside a home-built coin-sized permanent magnet. The transverse relaxation rates, R_1 were measured by standard Inversion-Recovery pulses sequences observed by Carr-Purcell-Meiboom-Gill train pulses. The transverse relaxation rates, R_2 were measured by standard Carr-Purcell-Meiboom-Gill train pulses (200 µs of interecho time) consisting of 2000 echoes. A total of 12 scans were typically acquired for signal averaging unless mentioned otherwise. All samples were measured at room-temperature. All data were acquired three times and reported as means. The transmitter power output is maintained at 360 mW for a single 90°-pulse of pulse length 6 µs, which correspond to nutation frequency of 41.6 kHz. A recycle delay of 1 s which was set between each pulse is sufficiently long enough to allow all the spins to return to thermal equilibrium.

IV. CONCLUSION

Such a rapid, ultra-sensitive and simple means of quantification enables study pharmacokinetics and pharmacodynamics, where the rate of assay is only limited to the incubation process. With the availability of such highly sensitive, and yet low-cost system at point-of-care, we hope to bring the MRR system to clinical settings in which effort in phenotyping of blood-borne diseases, drug/toxicity screening and so forth can be accelerated.

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