Magnetoresistance Sensor with Analog Frontend for Lab-on-Chip Malaria Parasites Detection

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***Abstract*—This paper presents a miniatured low noise, low power, and high-sensitive malaria diagnosis based on the magnetoresistance (MR) sensor with a CMOS analog front-end (AFE) readout circuit for the detection of paramagnetic hemozoin particles. *COMSOL Multiphysics*® is employed for the finite-element (FEM) simulation of hemozoin particles to prove that the magnetic field generated from a multi-hemozoin particles system is within the sensing range of MR sensors. A CMOS AFE circuit is designed to convert the tiny current from MR sensors into a strong voltage signal able to be sampled and suppress high frequency and large amplitude noises stemming from the shift of the resultant magnetic field during the malaria diagnostic process. This CMOS AFE circuit is composed of a transimpedance amplifier (TIA) and a pair of Butterworth filters. This TIA can achieve a 96.6 dB dc gain and a 2.041 MHz bandwidth with low power consumption (641.85 µW) at a 3.3 V voltage supply and low input-referred noise (54.6873 nA/√Hz at 100 Hz). Butterworth filters can significantly reduce the high frequency and large amplitude noises caused by the unexpected shift of the magnetic field. The experimental results prove that the system provides an immediate response to serum samples with hemozoin particles and has the potential to achieve an early low-density malaria diagnosis.**

Keywords: Butterworth filter, CMOS, early diagnosis, finite-element method, hemozoin, malaria, magnetoresistance sensor, paramagnetic, transimpedance amplifier.

I. Introduction

Malaria, caused by parasites, remains a major global health burden, particularly in malaria-endemic areas with low-resource around the world. Conventional methods such as microscopy, rapid diagnostic test and polymerase chain reaction are not suitable for these areas as they need advanced malaria diagnostic systems with cost-effective, low power, high-sensitive and point-of-care features [1]–[4]. This paper proposes a lab-on-chip malaria diagnostic system based on a magnetoresistance (MR) sensor and a CMOS analog front-end (AFE) circuit for the early detection and intervention.

Hemozoin, a by-product from the digestive system of malaria parasites, indicates a remarkable and distinctive paramagnetic property in the infected red blood cells (iRBC). Thus, magnetic immunoassay based on hemozoin is regarded as one of the most promising candidates for malaria diagnosis [5], [6]. Compared with traditional magnetic-based methods such as expensive and bulky nuclear magnetic resonance and superconducting quantum interference devices, etc. MR sensors have the advantages of small physical size, low power, high sensitivity and CMOS compatibility [7], [8]. Over the past decades, giant magnetoresistance (GMR) and tunnel magneto-resistance (TMR) sensors have been widely utilized in non-clinical applications such as the detection of Influenza A Virus [9]–[14]. Due to the higher sensitivity than GMR [15], the TMR sensor offers more possibilities to achieve ultrasensitive hemozoin detection and early malaria diagnosis for the prevention of possible malaria pandemic.

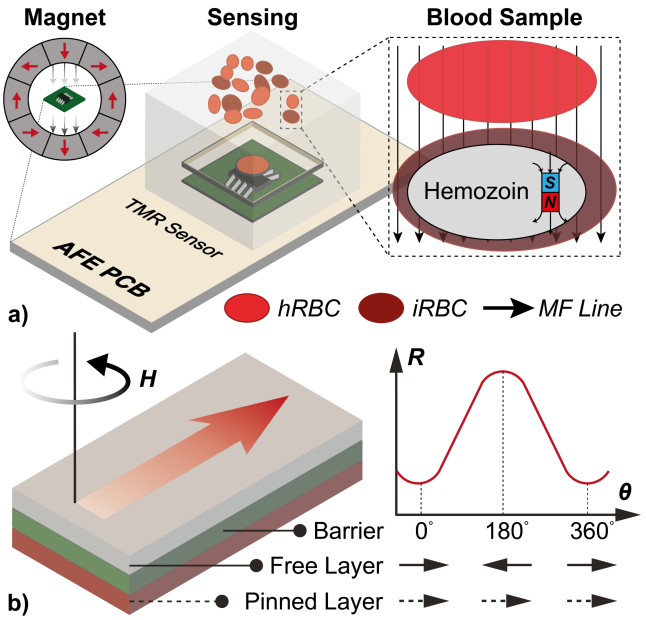

Fig. 1. The overview of tunnelling magnetoresistance sensor-based malaria Parasites Detection system, including TMR sensor; Magnet: Halbach array; AFE: analog-front-end; PCB: printed circuit board. Red arrows represent the magnet magnetization directions and MF is generated magnetic field lines by Halbach array. hRBC and iRBC present healthy and infected red blood cells. (b) The basic structure and transfer curve of the TMR sensor.

The principle of the proposed malaria diagnostic system is exerting an external magnetic field to induce the magnetic field variation of hemozoin particles with the paramagnetic property. The resistance of the TMR sensor is linearly varied as a function of the resultant magnetic field in the linear operating region. The direction of the external magnetic field is adjusted to keep the sensor operating in its linear response region with high sensitivities before each test. Here, the phase difference of the magnetization orientation between the free layer and the pinned layer is orthogonal. When the external magnetic field is applied, hemozoin particles will generate a weak magnetic field, which will be diverted to be parallel with the applied magnetic field. The MR sensor can sense the resultant magnetic field variation in the linear region and change its resistance with the addition of hemozoin. Fig. 1(a) illustrates the sensing process of malaria. The permanent magnet in this system is a one-tesla Halbach array producing a uniform magnetic field at the center of the magnet, where the TMR sensor is placed. The sensing core of this system is the TMR sensor integrated with a CMOS AFE circuit. iRBC with hemozoin, different from healthy red blood cells (hRBC) in serum samples, will provide an immediate response to the magnetic field. Fig. 1(b) presents

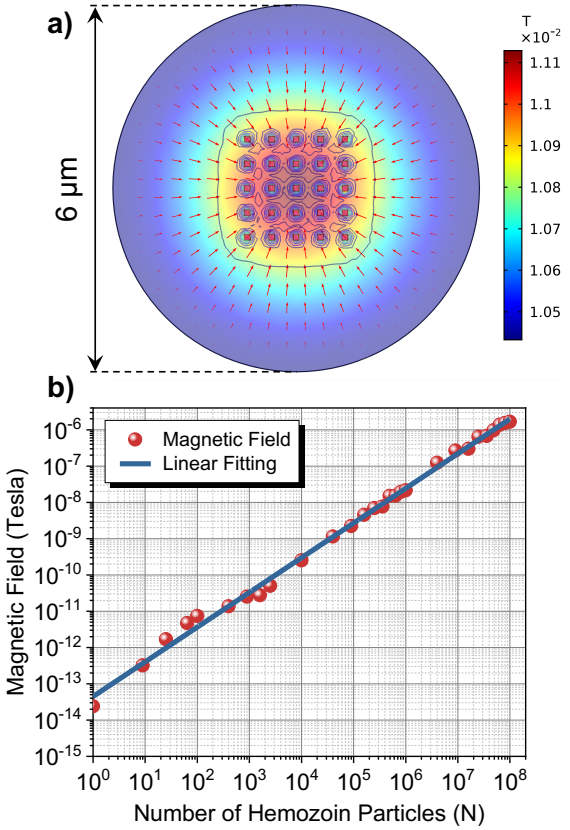

Fig. 2. (a) Total Magnetic field produced by 5 × 5 hemozoin particles matrix (*x*-*z* plane), where the distance between two adjacent hemozoin particles is 300 nm. The magnetic field directions generated from all hemozoin crystals are heading in the same direction with the applied magnetic field (*y*-axis). (b) The relationship between the number of hemozoin particles and magnetic fields produced by hemozoin at 1.5 mm distance (*y*-axis) with an n-order identity matrix of 0 nm distance distribution.

the sandwich structure of the TMR sensor and a phase-varying function of the resistance in the TMR sensor. The resistance of the TMR sensor is determined by the phase difference of the magnetization orientation between the free layer and the pinned layer, the magnetization orientation of the pinned layer is fixed. In contrast, the magnetization orientation of the free layer will rotate and follow the magnetic field direction of the resultant magnetic field from the permanent magnet and hemozoin. Eventually, the MR sensor will decide the healthy condition of unknown blood cells, iRBC with hemozoin will provide a weak stimulus for the TMR sensor to produce a current variation.

The proposed system consists of two parts: (1) Malaria hemozoin sensing and (2) Sensor readout. The TMR9001 (TMR 9001, MultiDimension Technology) was implemented with a sensitivity of 300 mV/V/Oe and limit of detection of 150 pT/√Hz. The overview of the proposed detection system with a full-bridge Wheatstone configuration is illustrated in Fig. 3. Three amplifiers are employed to magnify the weak output signal from the MR sensor into a robust signal. The first amplifier functions as a transimpedance amplifier (TIA) converting the weak current variation into a voltage signal simultaneously. The noises in this system mainly stem from the unexpected shift of the magnetic field, mainly attributed to the unpredicted movement of the strong magnet and the blood sample with hemozoin. Besides, the pressure and touch on the TMR sensor will generate an impulse noise. Most noises are composed of high frequency and large amplitude signals. The signal from the sensor is so weak that noises will significantly affect the results. Fortunately, the signal from the TMR sensor is a DC current. For noise cancellation, the remaining two parallel and identical voltage amplifiers are Butterworth amplifiers performing as active low pass filters. Finally, an analog-to-digital converter (ADC) is utilized to convert the analog signal into digital information which can be read by the user interface. The experimental results prove that this system can obtain a very clean signal.

II. Architecture Overview

This section consists of two components: magnetic field simulation of hemozoin and analog signal processing circuit design. The simulation is to prove the feasibility of the proposed system and to find a proper analog signal readout on-chip system for analog signal acquisition and processing.

A. Hemozoin Simulation

The magnetic field simulation of hemozoin includes the magnetic interaction between single hemozoin particles and the magnetic field generated from a multi-hemozoin system at a distance. Simulations are based on the magnetic field finite element (FEM) analysis. *COMSOL Multiphysics*® is adopted to create a magnetic field boundary condition and treat hemozoin particles as the paramagnetic material. There are two tasks of a finite element analysis: (1) The geometry modelling of the hemozoin particle. (2) The evaluation of the magnetic field produced by a multi-hemozoin system.

1) Interaction between Single Hemozoin Particles

The geometry of a single hemozoin crystal is a brick-like shape with *length:width:height* equaling to 100 nm:100 nm: 800 nm. The magnetic permeability constant of a hemozoin

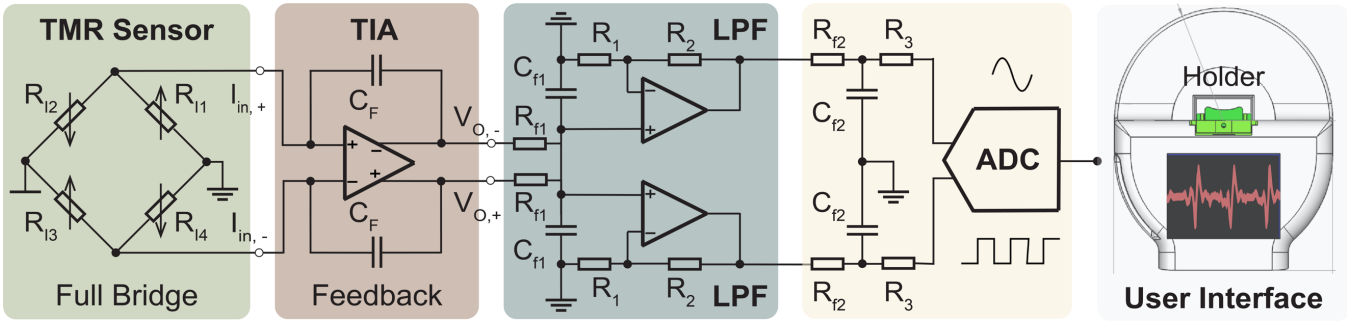

Fig. 3. A schematic diagram of the readout system. Tunnel magnetoresistance (TMR) sensor is a full-bridge Wheatstone structure with two current outputs. Transimpedance amplifier (TIA) with the capacitive feedback (C_F) topology will convert the current signal from the TMR sensor into voltage and amplify the signal simultaneously. A pair of Butterworth filters function as active low pass filters (LPFs) to cancel the high frequency noise from TIA and amplify the signal again. ADC is a two-input one-output structure to transfer the analog signal into a digital signal. User Interface is the point-of-care malaria diagnostic platform composed of the serum sample holder, Halbach array (external magneto) and LCD display module.

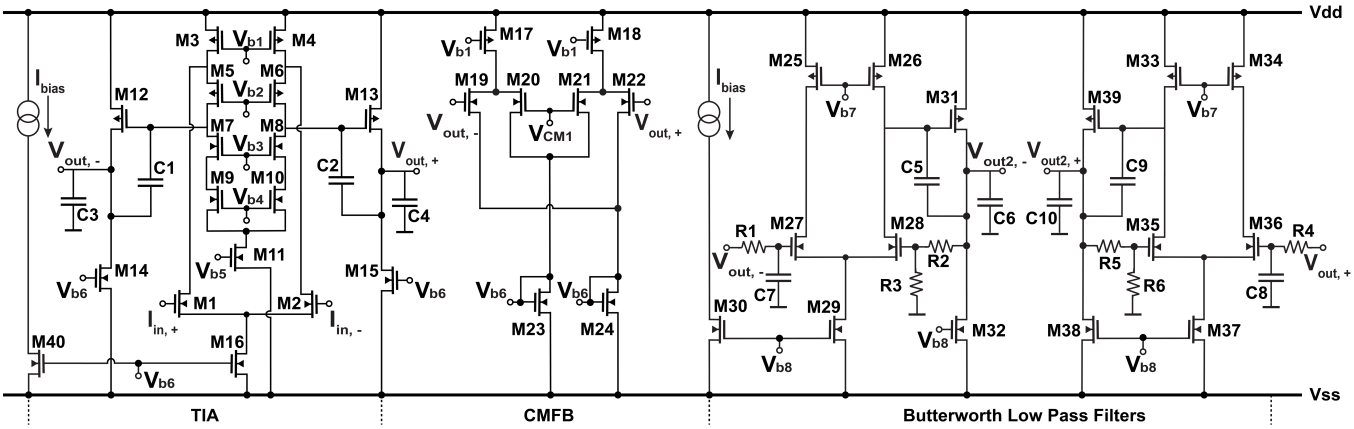

Fig. 4. A schematic diagram of the CMOS AFE circuit with a two-stage transimpedance amplifier, a common mode feedback and a Butterworth lowpass filter.

crystal is μ = 6783 at room temperature [16]. As is shown in Fig. 2(a), the magnetic field produced by a single hemozoin crystal will influence its adjacent particles because the strongest magnetic field generated at the center of a multi-hemozoin particles system will force hemozoin particles to move to the center. When an external magnetic field is applied, there will be a magnetic attraction among hemozoin crystals. The magnetic interaction between hemozoin crystals will lead to an agglomeration phenomenon in a multi-hemozoin particles system.

2) Magnetic Field of Multi-hemozoin Systems

The magnetic attraction was considered in a multi-hemozoin system. With the inducement of the external magnetic field, all hemozoin crystals will divert their original random magnetic field orientations to be parallel with the external magnetic field at an equilibrium state. A hemozoin crystals distribution for a multi-hemozoin system is shown in Fig. 2(a). Since the height of TMR 9001 package is 1.5 mm, the boundary condition of the magnetic field system is set to be a sphere with 1.55 mm radius. The multi-hemozoin system can exert a magnetic field at a distance with the magnetic attraction between hemozoin particles.

Fig. 2(b) shows the simulation results of the multi-hemozoin system with different numbers of particles. As the number of particles increases, the magnetic field produced by the system at 1.5 mm increases accordingly. The number of hemozoin particles in the human body depends on the amount of heme, the raw material for hemozoin formation. Thus, a significant number of hemozoin particles exist in infected serum samples. The magnetic field produced by the infected blood sample will be far greater than pico-Tesla level. The magnetic field produced by a cluster of hemozoin particles is within the sensitivity range of MR sensors [7].

B. Readout Circuit

A CMOS AFE circuit is designed to obtain a clean analog signal and a miniatured system. This system consists of transimpedance amplifier (TIA), common mode feedback (CMFB) circuit and two parallel identical Butterworth filters. This system ensures low noise to avoid the interference with the relatively low signal from MR sensors.

1) Gain-boosting Amplifier

The first stage of the Gain-boosting amplifier is a dual input folded cascade telescopic amplifier because of the dual output structure of TMR 9001. Compared to other amplifier topologies such as differential amplifier, the telescopic amplifier has high speed, low power and low noise. These advantages enable the telescopic amplifier to capture the instantaneous tiny variation output from TMR 9001, which ensures high sensitivity to the small hemozoin particles. The limitation of telescopic amplifiers is small output swing. The second stage is a fully differential output structure, compared to a single output, the fully differential output can achieve the larger voltage swing, stronger noise immunity, and higher gain as the complement with the first stage.

Miller frequency compensation method is adopted to ensure the stable operation of the gain-boosting amplifier. This structure utilizes Miller capacitors for the frequency compensation. The transfer function for this structure in the two-stage amplifier is shown in Eq. (1) [17]. By changing the value of the capacitor, the phase margin of the operational amplifier can maintain a stable state.

$$H(s) \approx \frac{C_{in}}{C_F} \cdot \frac{1 - s \cdot \frac{C_F}{A_V \cdot g_{m2}}}{\left(1 + \frac{1}{sR_F C_F}\right)\left(1 + s\frac{C_c C_{in}}{g_{m1} C_F}\right)} \quad (1)$$

where C_{in} is the input capacitor, C_c is the Miller compensation capacitor. g_{m1} and A_v are the transconductance and the gain of the first stage, respectively. g_{m2} is the transconductance of the second stage. R_F and C_F are the equivalent feedback resistance and capacitor of the gain-boosting amplifier.

2) Transimpedance Amplifier

This amplifier functions as a current-to-voltage converter because of a pair of feedback capacitors. Compared with the resistive feedback, capacitive feedback structure will cancel

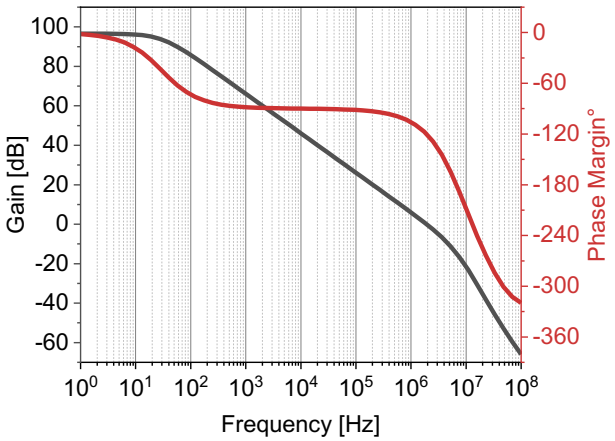

Fig. 5. The transimpedance amplifier results: gain and phase margin.

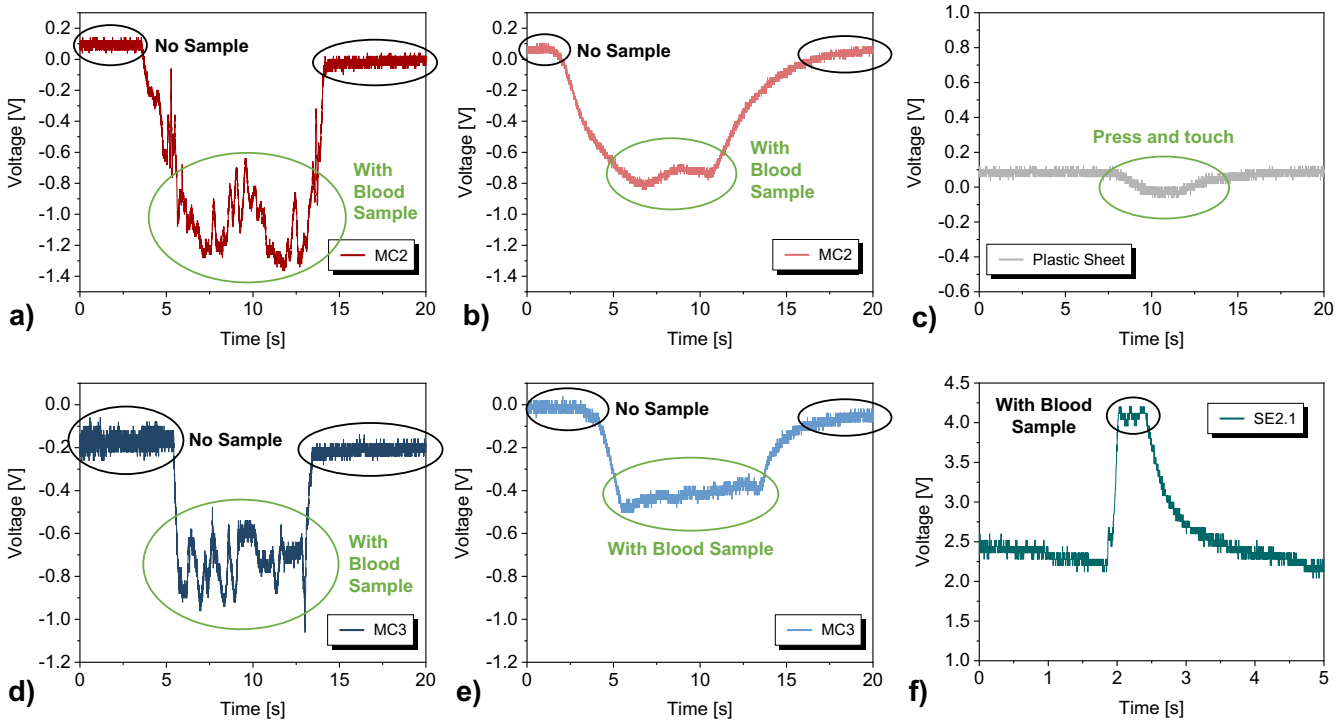

Fig. 6. Experiment results of samples containing hemozoin based on the proposed system. MC2 and MC3 are two serum samples of infected red blood cells. SE2.1 is the natural hemozoin sample extracted from malaria parasites. The plastic sheet is a plastic bag with only water. (a) and (d) are the results directly from TIA without filters. (b), (c), (e) and (f) are the results with Butterworth filters. (c) shows the result of plastic sheet with pressure and touch on the sensor.

the noise from resistors and function as an integrator, which enables this amplifier to enjoy a high transimpedance gain with low input noise. In detail, the current variation from TMR 9001 will accumulate on the feedback capacitor and form a significant voltage drop or increase, because the voltage on the feedback capacitor is a time-varying function of current. Furthermore, feedback capacitors function as low pass filters, as the frequency increases, the response of the integrator becomes smaller. Thus, capacitive feedback can suppress high frequency noises.

3) Common Mode Feedback Circuit

Despite the advantages of the second-stage differential structure in the gain-boosting amplifier such as large output swing and high gain, it suffers from the impact of the common signals mismatch. The CMFB circuit functions as a negative feedback circuit to stabilize the common mode output voltage and keep all transistors operating in the saturation zone. The CMFB circuit will compare the common mode output voltage from the full differential amplifier with a reference voltage, then return a feedback voltage to the amplifier to keep the output stable.

4) Butterworth Filter

The capacitive feedback in the TIA cannot remove the high frequency noise completely, because the amplitude of the high frequency noise is too large to suppress. The noises from the TIA mainly stem from the movement of the device during the diagnostic process, especially the displacement of the applied magnetic field and the MR sensors. These magnetic field displacements often cause high-frequency noises with high amplitude. Butterworth filters serve as active low pass filters and have a significant suppression capacity on high amplitude noise. The amplifier chosen for Butterworth filter is a two-stage single-input single-output differential amplifier. Thus, CMFB circuits are not required in a one-input differential amplifier.

III. Exprimental Results

The CMOS AFE circuit was implemented on TSMC 180 nm process. The power supplies on the TIA and two Butterworth filters are 3.3 V. The power consumption of the TIA is 641.85 μW. As is shown in Fig. 5, the DC transimpedance gain and the phase margin of TIA are 96.6 dB is 60.06 degrees respectively, and the gain-bandwidth product (GBW) is 2.041MHz. Results show that TIA is a high gain low power and stable amplifier with a GBW suitable for DC signal detection. Additionally, the TIA has 54.6873 nA/√Hz at 100 Hz input-referred noise, 74 dB CMRR and 303 dB PSRR. Thus, the TIA achieves a low noise amplifier with high sensitivity to hemozoin.

The experimental results in Fig. 6 show the responses of the malaria diagnostic system. By comparing results between the plastic sheet and samples with hemozoin, this system can detect the serum samples with natural hemozoin particles. Fig. 6(c) shows that influence of the pressure and touch on the TMR is feeble. By comparing the results between samples with and without Butterworth filters, most high frequency and high amplitude noises can be significantly reduced by Butterworth filters.

IV. Conclusion

Proposed handheld malaria diagnostic platform based on MR sensors can obtain clean readout signals from the serum samples with natural hemozoin particles and has the potential to achieve early malaria diagnosis. Simulations on hemozoin particles show that the magnetic field generated by hemozoin is within the sensing range of high sensitive MR sensors, early malaria detection is feasible by using TMR sensors. The designed CMOS AFE circuit achieves the low noise and high sensitivity capable and the experimental results prove that the system provides an immediate response to serum samples with hemozoin particles and has the potential to achieve an early low-density malaria diagnosis.

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