Portable Diagnostic Platform for Rapid Detection of 2µL Paramagnetic Particles in 5s

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***Abstract*—With the fast development of Tunneling magnetoresistance (TMR) biosensors, this paper reports a low noise, rapid, lab-on-chip system based on TMR sensors for malaria pigment (hemozoin) detection. A semiconductor circuit is designed to amplify the negligible (approximately 5mV) signal from the TMR sensor and to reduce the high frequency noise from the electronics. The semiconductor circuit is comprised of several Low drop-out (LDO) regulators, an instrumentation amplifier and an 8-order Butterworth ladder lowpass filter. In detail, this instrumentation amplifier reaches 90dB dc gain with 1 nV/√Hz low input noise at double ±5V voltage supply. The cut-off frequency of the lowpass filter is adjustable 0.1Hz to 50kHz, which can obviously reduce the noise from the environment and the electronics. *COMSOL Multiphysics®* is applied to simulate the infected red blood cell (RBC) as well as the external magnetic field. The simulation results certify the feasibility of the system, which provides a fast response to the hemozoin samples. The designed system can detect the liquid paramagnetic samples in real time.**

Keywords—Biosensor, hemozoin, paramagnetic, real-time, malaria, Butterworth filter, semiconductor.

I. Introduction

Malaria is an insect-borne infectious disease transmitted through the bite of an *Anopheles* mosquito infected with *Plasmodium spp*. Currently available malaria diagnosis methods have many limitations and drawbacks. e.g. Microscopy is time-consuming and requires well-trained microscopists, rapid diagnostic tests (RDTs) are not accurate enough for low parasite densities [1][2]. Thus, there is a growing need for effective detection of disease. This paper presents a lab-on-chip real time sensing system based on TMR sensors.

Hemozoin is a metabolically crystallized by-product of the digestion of haemoglobin by the parasite during infection of the red blood cells (RBCs)[3]. The average hemozoin dimensions are approximately 100nm×100nm×300–500nm, and an average parasite weighs 0.36-0.49pg[4]. Multiple research papers have reported on the paramagnetic properties of hemozoin particles[5][6], and a magnetic assay based around hemozoin is considered as a promising method for malaria diagnosis[7].

Applied magnetics biosensors utilize tunnelling magnetoresistance (TMR), which has developed rapidly in recent decades. Compared to earlier anisotropic magnetoresistance (AMR) and giant magnetoresistance (GMR) technologies, TMR sensors have better sensitivity (20mV/V/Oe) than GMR sensors (3mV/V/Oe) and offer

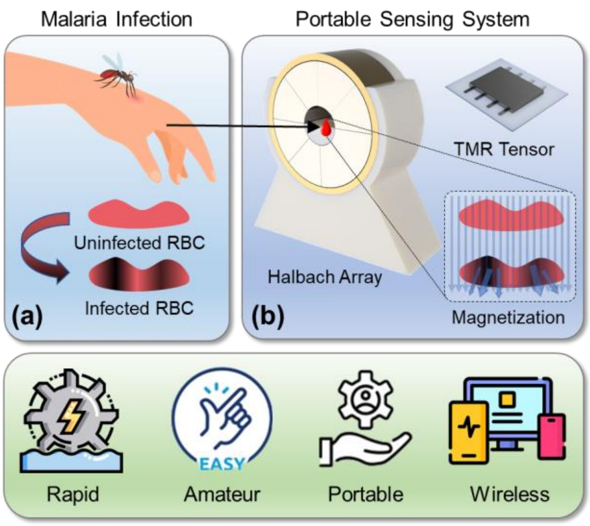

Fig. 1. Overview of lab-on-chip malaria detection system. (a) The change of red blood cells in the infection. (b) Elements in device.

improved detection of tiny paramagnetic particles such as hemozoin [8]. Furthermore, the working range of TMR sensor (0.001-200Oe) is also greater than the previous technology (0.01-30Oe).

The principle of lab-on-chip platform is to apply a 10kOe external magnetic field to magnetize the hemozoin particles exploiting their paramagnetic properties. The tiny magnetic field generated by magnetized hemozoin changes the orientation of the top layer of the TMR sensor, and thus the output from the sensor will change. In addition, the instrumentation amplifier as well as lowpass filter have been fabricated on printed circuit board (PCB), the signal is enhanced and the noise from external environments is reduced by the instrumentation amplifier and the lowpass filter respectively. Fig.1 (a) illustrates the transformation of red blood cellsfollowing infection... Fig.1 (b) shows the magnetization of different samples. In the detection of uninfected RBC samples, the output signal is low level voltage, once the infected RBC samples are detected, the signal is changed into high level voltage. The difference in voltage level will indicate whether infected RBC are present in the sample.

This paper is organized as follows: The finite-element (FEM) simulations of external magnetic and hemozoin are presented in Section II, while the system design is shown in Section III.

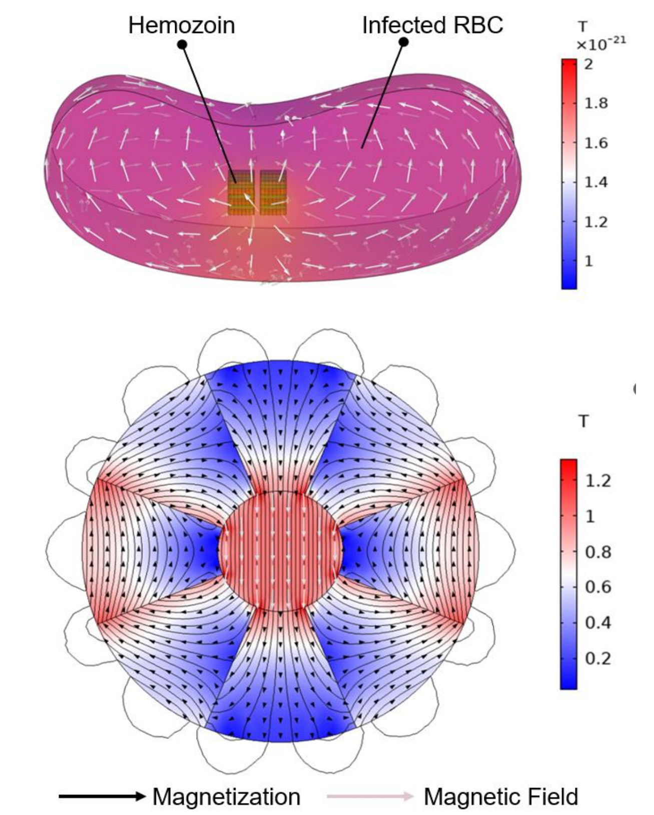

Fig. 2. Finite-element (FEM) Simulation. (a) Magnetic field of Hemozoin in infected RBC. (b) 8 Magnets Halbach Array generate 1T vertical magnetic field in the center.

The detection results are given in Section IV. Finally, Section V states the conclusion.

II. Simulation

To prove the feasibility of sensing system, *COMSOL Multiphysics®* is applied for finite-element (FEM) simulation. In this section, two structures are simulated: *A*. hemozoin in red blood cells, *B*. Halbach array.

A. *Hemozoin in red blood cells.*

During infection, malaria parasites produce hemozoin in the erythrocyte. Fig.2 (a) shows the infected RBC in external 1T downward magnetic field stimulation. The shape of human red blood cells is approximately 7.5 to 8.7μm in diameter and 1.7 to 2.2μm in thickness[9]; in this work, 8μm×2μm sized erythrocytes are simulated. Ten hemozoin particles are placed in the centre of the cell. 18 particles are simulated as brick-like with dimensions of 100nm × 100nm × 400nm [4]. Hemozoin is considered as an insulation material with the breakdown field larger than 5×10^7 V/m. Previous research has demonstrated the paramagnetic properties of haemozoin, and $\mu_r = 4.1\times10^{-4}$ is used as relative magnetic permeability and applied in the simulation at room temperature[10]. When the external 10kOe magnetic field are implemented, the paramagnetic particles are magnetized, which influences the whole cell. With the simulated amount of hemozoin, the induced magnetic field can be sensed by the designed system.

B. *Halbach Array*

The Halbach array is a unique combination of permanent magnets that increases the magnetic field on one side of the cylinder while eliminating the field to near 0 on the other side [11]. The number of magnets is not fixed: some have 8 magnets, some have 12. All Halbach Arrays have magnets arranged in circles in a particular way - the special layout can generate various magnetic fields. This paper applied a unique 8 NdFeB N45 magnet structure from *E-MAGNETS®* to generate a 10kOe magnetic field in the central of the circle. Each strong permanent magnet has a different direction of magnetization. Fig. 2 (b) draws the unique placement of magnets and their magnetization direction. The entire diameter is 9.5cm and 3cm for the central circle. While the sensor is placed in the middle, the magnetic field in horizontal direction is zero and the vertical direction is 10kOe downwards. Moreover, the periphery magnetic field is reduced to zero in this structure. Because of the interference of the geomagnetic field and other equipment, the horizontal magnetic field is non-zero in practice; thus, the rotatable Halbach array is also used for resetting the central magnetic field to zero.

III. System Design

This section explained the details of circuit and platform construction. The presented platform are comprised of two parts: *A*. TMR Sensor. *B*. Amplification. *C*. Noise Reduction. *D*. Analog and Digital Display. *E*. 3D printing platform.

A. *TMR Snesor.*

Tunnel magnetoresistance (TMR) is a magnetoresistive effect that happens in a magnetic tunnel junction (MTJ). It was firstly observed in 1975 by Michel Jullière in Fe/Ge O/Co-junctions at 4.2 K. [12] A MTJ element consists of a pinned layer, a tunnelling barrier, and a free layer. In detail, the pinned layer is in the middle of the architecture and fixed while the free layer can rotate as themagnetic field changes. TMR sensors, which have been developed over the past decade, have good potential for sensing tiny magnetic fields. In this work, TMR 2922 (*Multidimension Technology®*) is applied with 7~15mV/V/Oe sensitivity and 1nT/rt (Hz)@1Hz low noise spectral density. Fig. 3 (a) illustrates the sensor with 4 linear elements, which are comprised of a special structure called a Wheatstone bridge. Each element is variable in resistance in order to change the bias voltage in the Wheatstone bridge as well as the final output. The formula of the output is shown in Eq. (1).

$$V_{TMR} = V_{Power}\left(\frac{R_2}{R_1+R_2} - \frac{R_4}{R_3+R_4}\right) \quad (1)$$

If a horizontal magnetic field is detected by the sensitive elements, the resistance of R1&R4 increase while R2&R3 decrease. This unique structure could provide a high sensitivity voltage output. Moreover, this design can also provide an excellent temperature compensation for the output. The package size is around 1cm^2 which is suitable for placing in the Halbach array. Once the paramagnetic samples are placed on the sensor, the output changes from low level voltage to high level voltage. Benefiting from the small SOP-8 package, this sensor can be placed and fixed in the central of Halbach array.

B. *Amplication.*

Since the sample volume is small, the signal of sensor is not readable before the amplification, an instrumentation amplifier (AD8429 *Analog Device®*) is thus implemented. It performs well in amplifying extremely small signals over

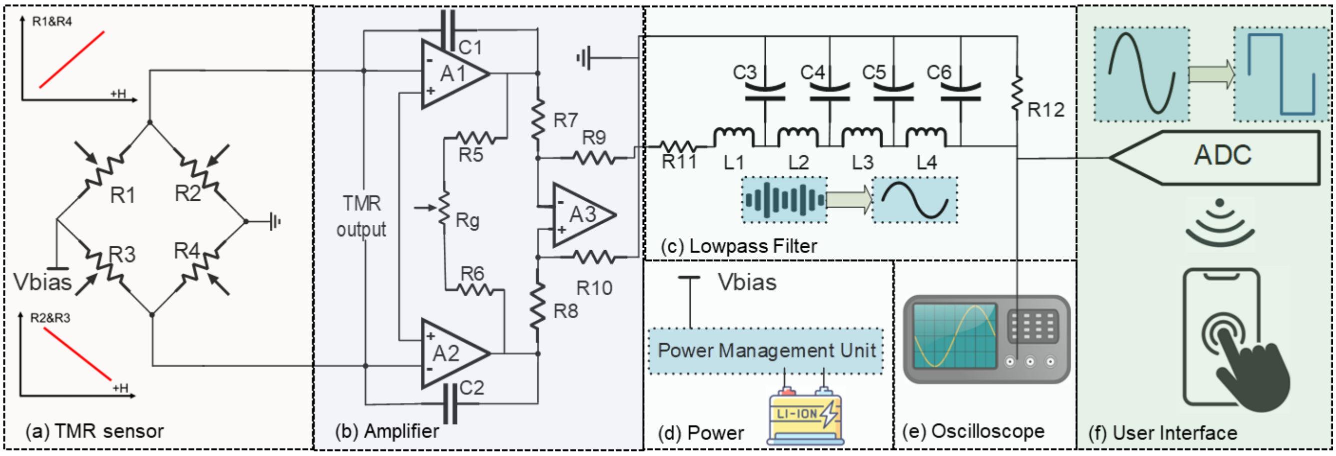

Fig. 3. Schematic diagram of lab-on-chip sensing system. (a) TMR sensing circuit. (b) Amplification circuit. (c) noise canceling circuit. (d) Power management unit. (e) Analog oscilloscope display. (f) Analog to digital converter and digital interface.

high temperature range. The dc Gain can reach 90dB by adjusting the resistance connected to the amplifier, as shown in Fig.3 (b). This amplifier consists of 2 input buffers and a differential amplification unit. The transfer function is shown in Eq. (2).

$$V_{OUT} = G \times (V_{IN+} - V_{IN-}) + V_{REF}$$

Where $$G = 1 + \frac{6k\Omega}{R_g} \quad (2)$$

V_{IN+} and V_{IN-} indicates the TMR output, denoted the differential signal, and V_{REF} is connected to the common ground in this circuit. This type of differential amplifier achieves high SNR DC signal output with less AC noise. Additionally, it delivers ultra-low input noise performance of 1nV/√Hz and owns a high common mode rejection ratio (CMRR) to prevent interfering signals from destroying data acquisition. Considering the tiny DC signal from the sensor, the G has been set to 1000 in the circuit, where R_g=6Ω. In this work, the output can be amplified from 1mV to around 1V. Furthermore, this amplifier requires ±5V Voltage supply to work, which indicate a dual Voltage supply unit with both positive and negative is needed. The SOIC-8 package allows the soldering in printed circuit board (PCB).

C. Noise reduction

The noise of this system comes both from the environment and electronics. Environment noise such as geomagnetic field is usually constant or at low frequency, which can be cancelled manually by adjusting the angle of Halbach array. The high frequency component noise from electronics is reduced by the 8-order Butterworth lowpass filter (MAX291 *Analog Device®*). This ladder- shaped filter shown in Fig.3 (c) can manually set the cutoff frequency from 0.1Hz to 50kHz. The filter is comprised of several capacitors, inductance and resistors. Since the desired signal is a DC signal, the cutoff frequency is set to 0.1Hz with less than 1 second delay. Furthermore, this filter also works with the dual ±5V Voltage supply and can be fabricated in PCB.

D. Power Management Unit.

Several components require dual voltage supply in the system. Hence a low noise, smooth power supply is very important, as this directly affects the stability of the entire equipment. A low-dropout (LDOs) regulator is a DC linear voltage regulator that can regulate the output voltage even though the supply and the output voltage are of similar magnitude [13]. As illustrated in Fig.3 (d), TPS65133 (*Texas Instrument®*) is implemented in PCB, which can transfer a single 3.7V Li-Polymer battery (Mikroelektronika®) into dual ±5V supply for the amplifier as well as lowpass filter. Furthermore, the TMR sensor is connected to another LDO which provides 1V voltage as a typical value.

E. Analog and Digital Display.

The output signal is considered as an analog signal which can be collected and displayed on an oscilloscope. Benefiting from the DC signal and high performance lowpass filter, the oscilloscope can display a clear signal. A digital signal is more convenient in microcontroller during subsequently processing. The 10bit-AD converter shown in Fig.3 (f) is implemented to sample and transfer the signal. After the digital signal processing, the user can observe the system output and distinguish whether the samples are infected or not. Subsequently, the signals are extracted, classified, and displayed in a LabVIEW interface on a laptop.

F. 3D printing Platform.

The detection system setup is shown in Fig. 4. In order to minimize the external magnetic influence of device, the ABS material is employed. The 3D printing model holds the TMR sensor in the middle of the rotatable Halbach array, the PCB is connected with hard wires through the back of the model, while the oscilloscope is directly connected to the PCB output. Benefiting from the portable and handheld model, the samples can easily be placed above the sensor. The liquid samples (*MagneSil®*) used here are paramagnetic particles placed in 2mm thick plastic tube. The samples consist of 5% iron trioxide, 59% guanidinium chloride and 36% water.

IV. Experiment Results

The experiment system is set up as shown in Fig.4 at room temperature 295°K. The test sample contains 2uL opaque paramagnetic liquid and 2μL water was used as a reference. Fig.4 shows the comparison of the signal obtained with the sample and water. After adjustment of the central magnetic field manually by rotating the Halbach array, the data are

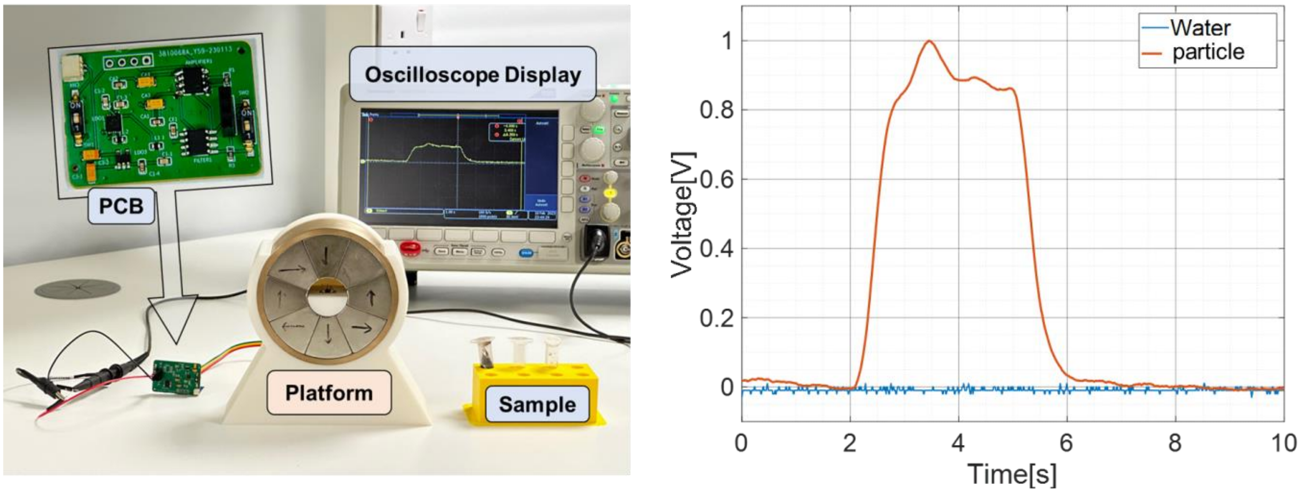

Fig. 4. The 3D printing platform design and processed experiment results.

collected and observed in an oscilloscope. Once the samples are presented and held above the sensor, the output signal changes from low level to high level, while there is no change in the presence of water or air. Each tube is held for two seconds and the total duration of each experiment is ten seconds. The sampling rate of oscilloscope is set at 1kHz, thus, a data set of 10k values is collected. In processing, *MATLAB®* is employed for data smoothing and normalization, the smoothing and normalized factors are set to 0.01 in advanced. Each sample was tested three times in order to estimate the size of measurement errors .

V. Conclusion

In this work, we have investigated a novel detection method for the potential detection of the paramagnetic material haemozoin using state-of-the-art magnetic sensors. Haemozoin is a feature of malaria parasites in red blood cells.To detect the tiny signal expected from samples of paramagnetic particles, linear tunnelling magnetoresistance (TMR) sensors were implemented. We developed with the packaged TMR sensor with sample holder, designed a circuit with a Wheatstone Bridge configuration in a printed circuit board level, completed PCB fabrication and soldering of each component, and validated circuit performance by experiments using paramagnetic particles to simulate infected RBC.

In finite-element (FEM) simulation, we simulated the infected red blood cell containing hemozoin within the Halbach array in *COMSOL Multiphysics®*. With the 10kOe magnetization in the center of Halbach array, the infected erythrocytes were predicted to generate a weak magnetic field.

In experiments, 3D printing technology was applied to build a portable platform to hold the samples. 2μL paramagnetic liquid samples were compared with 2μL of water as reference. After adjusting the system, a significant high voltage change was observed in oscilloscope when the samples were tested, whereas the output remained at a low voltage level otherwise.

Finally, using the acquired data in oscilloscope, the data smoothing and normalization was done in *MATLAB*.

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