Proceedings of the 2020 Design of Medical Devices Conference
DMD2020
April 6, 7-9, 2020, Minneapolis, MN, USA

DMD2020-9054

MAGNETIC PARTICLE SPECTROSCOPY-BASED HANDHELD DEVICE FOR WASH-FREE, EASY-TO-USE, AND SOLUTION-PHASE IMMUNOASSAY APPLICATIONS

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ABSTRACT

In recent years, magnetic particle spectroscopy (MPS) has emerged as a new technology for immunoassay applications. In MPS, alternating magnetic fields are applied to magnetic nanoparticles (MNPs). The magnetic responses of these nanoparticles are collected and recorded by a pair of specially designed pick-up coils. These magnetic responses contain higher harmonics that are specific to the physical changes of the nanoparticles such as the binding events of target analytes to nanoparticles. This volumetric-based bioassay method analyses the response signal from the whole nanoparticle suspension, thus, allows one step and wash-free immunoassay with minimum technical requirements. In this work, we developed a handheld MPS system as a future highly sensitive, cheap, in vitro, and easy-to-use point-of-care (POC) detection kit.

Keywords: magnetic particle spectroscopy, magnetic nanoparticle, harmonics, handheld device

1. INTRODUCTION

Since the pioneering work of Gleich and Weizenecker in 2005[1], magnetic particle imaging (MPI) has emerged as a new imaging modality that directly detects magnetic nanoparticle (MNP) tracers using alternating magnetic fields. At the same time, magnetic particle spectroscopy (MPS), a derivative technology of MPI, has emerged as a novel immunoassay tool that filled the gap of wash-free, easy-to-use, and portable home healthcare market[2–4]. MPS can be interpreted as 0D MPI where bi-directional sinusoidal magnetic field is applied to a suspension of MNPs. The magnetization of MNPs relax in response to the external magnetic field through Brownian and Néel relaxations. These MNPs are specially designed and coated with antibodies that specifically recognize and bind to target analytes from biofluid samples. Due to the nonlinear magnetic responses of these MNPs, higher harmonics are picked up by a pair of specially designed pick-up coils (see Figure 1). These harmonics can be easily extracted by means of appropriate filtering and are indicators of the physical environments of MNPs such as viscosity[5–7] and temperature[8,9] of the liquid medium as well as the binding events of target analytes onto MNPs. Since the biological tissues and fluids are nonmagnetic, there is negligible magnetic background noise from biological samples. MNPs are the sole sources of magnetic responses from testing samples and this volumetric-based immunoassay tool allows for minimum sample preparation.

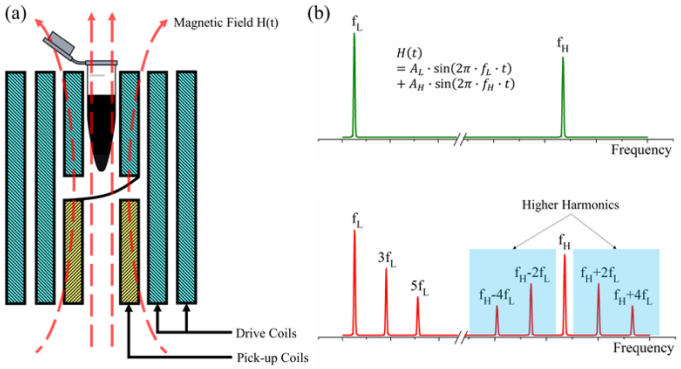

Figure 1. (a) Schematic view of drive coils, pick-up coils, and MNP suspension sample in plastic vial. Alternating magnetic fields are generated by drive coils. Magnetic responses of MNPs are picked up by a pair of pick-up coils. (b) The spectra of driving fields (green, top right figure) and MNPs (red, bottom right figure). Higher harmonics are induced by the nonlinear magnetic responses of MNPs.

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Currently, the commercially available disease diagnosis systems such as ELISA and Luminex are bulky in size, expensive and highly rely on technicians as well as daily equipment maintenance. The aforementioned factors make them impossible to popularize as advanced immunoassay technologies. Furthermore, disease diagnosis is unaffordable for people living in poor regions and developing countries. In 2018, Rabehi *et al.*[10] reported a MPS system for lab-on-chip pathogen sensing. Although their experiments to validate the magnetic bioassay and circuit board structure are in progress, the preliminary results on calibrating MNPs look promising. Herein, we are developing a MPS handheld device (see Figure 2) to mitigate the health burden in these regions and early diagnosis of diseases can effectively prevent the spread of infectious diseases as well as saving more lives. This device can be used indoors and outdoors such as research centers, medical clinics, at homes, and on fields. It provides users with an inexpensive and easy-to-use monitoring system. For individual users such as patients who need daily monitoring of chronic diseases, our MPS device provides them with everyday diagnosis at home. For clinics, hospitals, and pharmaceutical industries, it will help reduce expenses on laboratory and maintenance expenses.

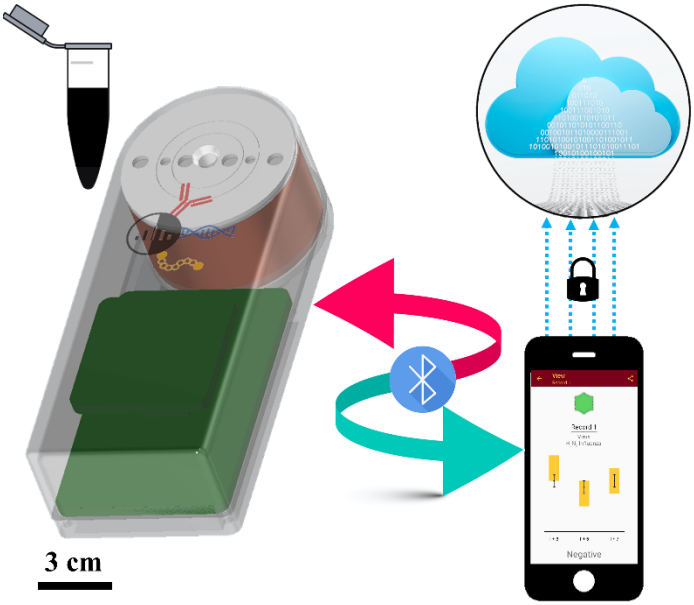

Figure 2. The MPS handheld device communicates with smart phone through Bluetooth. User data is synchronized and securely transmitted to the cloud storage.

2. SYSTEM ARCHITECTURE

Our developed MPS handheld system consists of five stages as shown in Figure 3: (1) Power, which generates usable DC voltages from Off-board AC power supply to be used by multiple Digital and Analog system components, (2) Control Unit, housing a microcontroller to deal with the computation requirements of the MPS handheld system, (3) Drive Coil Excitation, this stage constitutes of circuit for generation of two variable frequency sinusoids for excitation of primary and secondary drive coils (see Figure 1), (4) Signal Conditioning, which deals with signal conditioning on differential output from pick-up coils, and (5) Connectivity and Processing, comprising of Bluetooth and USB modules for proper transmission of high-frequency data to a mobile application for data processing and interpretation. A brief description of the aforementioned stages is given in the sub-sections below.

2.1 Power System

The power system consists of an off-board AC to DC power supply adapter to provide 24V DC supply (ALITOVE AC 100-240V to DC 24V 5A), voltage is further dropped down using high current rated linear drop-off (LDO) regulators and switching power supply components for providing a stable supply at suitable voltages to be used by different stages of the hand-held system. LM27762, a charge-pump based LDO from Texas Instruments (TI) is utilized to generate +/-2.5V supply and LM2990, TL751M05, linear LDO from TI are used to generate -5V and +5V supply voltages. LM2576 is a switching supply voltage regulator from TI which is used to generate a +3.3V supply voltage to power the onboard microcontroller. Switching regulators LTC7149 and LT3972 from Analog Devices (ADI) are used to generate -15V and +15V supply to feed the Drive Coil Excitation stage mentioned below.

2.2 Control Unit

A 32-bit microcontroller with built-in floating-point hardware from Microchip, PIC32MZ is utilized as the on-board processor. Microcontroller communication to ADC and Bluetooth module is built using SPI protocol. The microcontroller is also used for selecting variable frequencies for Primary and Secondary Drive Coils, using SPI protocol to communicate with digital potentiometers for selecting appropriate excitation frequency. IC AD5270 from ADI is utilized as a digital potentiometer for variable frequency signal generation.

2.3 Drive Coil Excitation

This stage generates two variable frequency sinusoids necessary for Primary and Secondary Drive Coil excitation. Sinusoid generation scheme can further be broken down into two sub-stages, namely (1) Wien-Bridge Oscillator and (2) Gain Amplifier and Buffer. Wien-Bridge Oscillator sub-stage generates a base sinusoid signal to be further processed by later stage. OPA320S from TI has been used to realize an Operational amplifier-based variable frequency Wien-bridge oscillator[11]. Gain Amplifier and Buffer substage amplifies incoming sinusoid and comprises of buffer circuit to meet with high current requirements of Drive Coils. OPA189 and OPA548 from TI are utilized for implementation of gain amplifier and high-current buffer stages respectively.

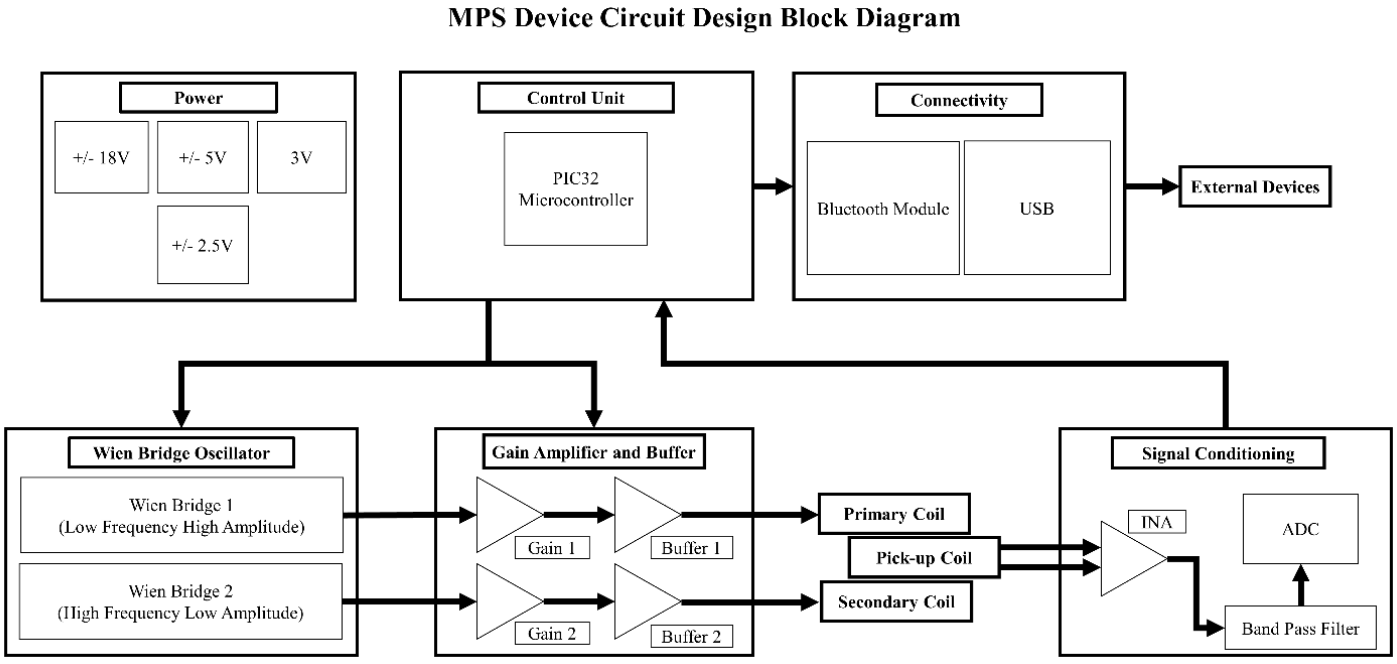

Figure 3. MPS device circuit board design block diagram.

2.4 Signal Conditioning

Pick-up coils generate differential voltage output which is conditioned for noise removal and amplification at this stage. INA128 from TI is being utilized as an instrumentation amplifier to provide an initial gain and convert the differential signal from search coils to a single-ended signal for further processing by filtering stages. OP07 from TI is utilized to realize Sallen-Key based second-order low-pass and high-pass filtering stages to remove the powerline and high-frequency noises. The cutoff frequency of the band-pass filter is set at 53 KHz for the low pass and 730 Hz for the high pass stages. The filtered signal is sampled at 200 KSPS with 16-bit samples using an ADC ADS1675 from TI which communicates with PIC32MZ microcontroller using SPI protocol. Microcontroller transmits data sampled by ADC using Bluetooth interface described in the following section.

2.5 Connectivity and Processing

An Android application has been developed to process information from the microcontroller in real-time and also to guide users on how to use MPS hand-held system (see screenshots of the user interface in Figure 4). 4.19 million-point Fast Fourier Transform (FFT) has been implemented for frequency-domain processing of incoming information. FFT implementation in the mobile application has been thoroughly tested and benchmarked, and it takes about 1.3 sec to perform 4.19 million-point FFT in real-time and give appropriate result. The frequency harmonic amplitudes and phase information is acquired from the FFT result to be used in deriving immunoassay detection. The harmonic amplitudes, phase angles and harmonic ratios are metrics for quantifying the target analytes from testing samples[2,12–16].

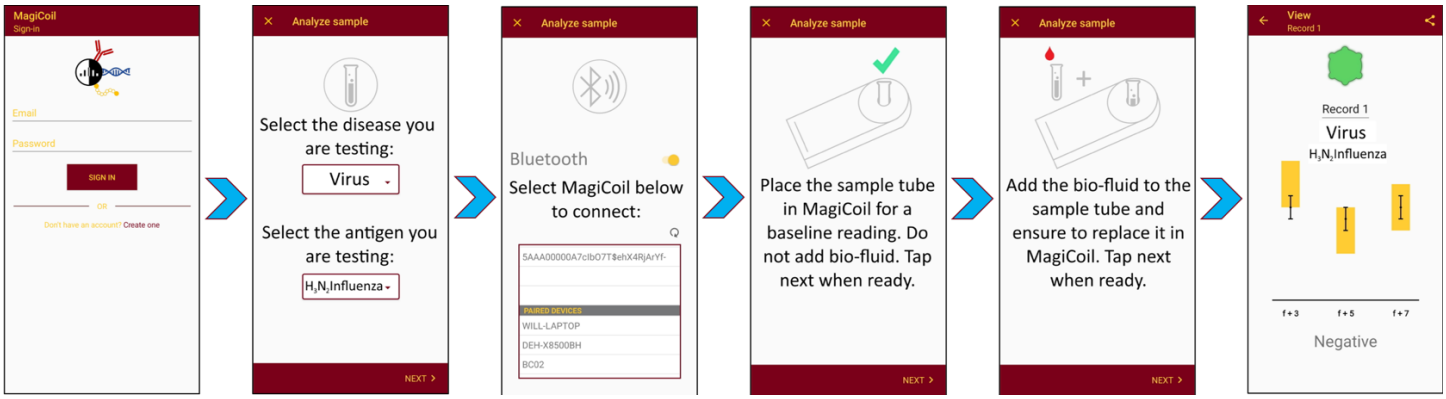

Figure 4. MPS mobile application interface gives user step-by-step instructions on conducting immunoassays.

3. DISCUSSIONS AND FUTURE PERSPECTIVES

In summary, we report here the systematic and circuit board design of the MPS handheld device. The most appealing aspects of this device are its versatile bio-sensing ability, simple process, portability, and its ability to communicate wirelessly with mobile devices. This handheld device provides users with a convenient, fast, and easy-to-use diagnostic tool. The future prospects of this work include development of an IOS application to extend services to a broader user base as well as development of a web-server for resolving the memory issue which limits the higher resolution FFT at present, this would also enable users to share the real-time and long-term monitoring information with his/her medical provider empowering remote disease diagnostics. This device is a platform technology and could be used for different disease detection and multiplexed immunoassays using just one sample (e.g. a drop of body fluid) in a single test.

ACKNOWLEDGEMENTS

The authors thank former team members contributing to the development of this MPS system, which can be found at: https://magicoil.ece.umn.edu. This study was financially supported by the University of Minnesota through the UROP program, the Institute of Engineering in Medicine of the University of Minnesota through FY18 IEM Seed Grant Funding Program.

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