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FABRICATION AND CHARACTERIZATION OF RADIO-FREQUENCY SENSORS FOR LIQUID MATERIAL DETECTION

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FABRICATION AND CHARACTERIZATION OF RADIO-FREQUENCY SENSORS FOR LIQUID MATERIAL DETECTION

A Thesis
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Master of Science
Electrical Engineering

by
Yuxi He
August 2013

Accepted by:
Dr. Pingshan Wang, Committee Chair
Dr. L. Wilson Pearson
Dr. Xiao-Bang Xu
ABSTRACT

This thesis presents a series of studies on fabrication and characterization of radio-frequency (RF) sensors. In the light of Electromagnetics and Transmission Line Theory, we designed multiple RF sensors with different detection capability emphasis and used them to detect various materials, especially liquid samples and materials in solutions such as dielectric thin films, confined liquids, red blood cells, and malarial pigments (hemozoin). Most sensors were fabricated under clean room environment following the standard process protocols. Proper process developments were also made to achieve special structures and functionalities of our novel sensors. Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM) were used to inspect and control fabrication quality. The main characterization techniques we applied include on-chip interference process, RF signal cancellation, micro/nanofluidics, single cell manipulation, and electron paramagnetic resonance (EPR). Through the whole process, sensors and measurement systems have been adjusted constantly and the characterization capabilities have been optimized. Our measurements and analysis have proved that RF sensors based on transmission lines could be very powerful detection tools comparing with other approaches currently in use for chemical and biomedical materials on both bulk and molecular levels. The main strength of RF sensors resides in the fact that they are able to work cost-efficiently, non-invasively and fast without involving powerful microscopy tools. Meanwhile, they promise to provide large amount of information with high sensitivity and resolution. Further work is needed to enhance the sensors’ capabilities quantitatively and expand the usage to additional applications.
ACKNOWLEDGEMENTS

My deepest appreciation goes to my advisor, Dr. Pingshan Wang for his invaluable inspiration and guidance through this entire study. Dr. Wang’s knowledge and insight on microwave and radio frequency studies have deeply influenced me and directly led to the accomplishment of this research. His trust and encouragement also have been helping me overcome difficulties and adversities.

I would like to express my sincere gratitude to my committee members, Dr. L. Wilson Pearson and Dr. Xiao-Bang Xu for guiding me on both course works and research. Their profound insight and professional attitude towards academics have significant influence on my academic pursuit and personal development.

I would like to extend my gratitude to many friends and colleagues here in ECE Department at Clemson University. I appreciate Mr. Jiwei Sun’s valuable suggestions on my research and generous help in life. The help and advice from our former group members: Dr. Chunrong Song, Dr. Hanqiao Zhang, Dr. Yang Yang, Dr. Chaojiang Li, and Mr. Yongtao Geng are appreciated as well.

Last but not least, I would like to thank my husband, Yida, and my parents for their unconditional support and love as always.
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CHAPTER 1

INTRODUCTION

Microwave techniques have become powerful and economical approaches to detect and analyze fluidic samples. Among the various microwave approaches, measuring the dielectric properties is one of the most important methods and forms the basis of dielectric spectroscopy, which has already been widely used to characterize the relaxation time of different samples, such as alcohol, acetone, petroleum, and etc. Dielectric spectroscopy is also useful in analyzing biological materials and entities, including blood components, cell suspensions, protein or DNA solutions and tissues.

Apart from its characterization capability, dielectric spectroscopy is known for its label-free and non-invasive detection. Before this idea was brought up and developed, optical observations and DC measurements have been the main approaches for the studies of molecules and cells in aqueous solutions. The former needs fluorescent labeling while the latter only provides limited information contents. However, broadband dielectric spectroscopy tools such as transmission lines and metallic electrodes, incorporated with microfluidic channels, can provide the missing information and minimize the intrusion at the same time. The integration of microfluidic channels with different electrical structures has generated many novel characterization ideas and applications, thanks to the rapid growth of bioelectronics. Moreover, the extension of the measurement bandwidth has produced a drastic increase in information contents that could be obtained.
This chapter covers the backgrounds of several research topics of interest. As an introduction, the current research efforts and techniques being in use are illustrated comprehensively in the next subsections. By examining the present techniques, we found the motivations and target problems to resolve. In the long run, the goal will be to develop new methods that can overcome technology difficulties and imperfections faced by the present techniques.

The outline of this thesis is also presented in this chapter.

1.1 Thin Film Dielectric Imaging

Measuring the local dielectric properties of thin films in liquid is an important technique for biomedical studies. For instance, recording the change of cell membrane capacitance is an established approach for exocytosis and endocytosis investigations. Patch clamps [1] are currently the standard method for such measurements, for which planar patch clamps [2, 3] have been developed in recent years for operation automation. The patch clamp technique allows the study of ion channels in cells, which can be applied to different kinds of cells such as neurons, cardiomyocytes, and muscle fibers. Patch clamp techniques normally use a glass micropipette to attach to the target cell membrane and record from a single or multiple ion channels. Here suction is applied to form a high resistance seal between the membrane and the pipette, which provides mechanical stability and electronically isolation to the outside area. Inside the pipette, there’s a solution with the ionic composition matching the cytoplasm and an electrode is placed in the solution conducting electric current to an amplifier. In this way, information of this specific membrane domain can be collected exclusively. However, patch clamps are slow
and intrusive with sensitivities and spatial resolutions insufficient for detailed cell membrane characterizations. It also requires strict experiment environments.

Various scanning microscopes, which are usually based on AFM-type of probe control, do not have such limitations. They may be used for cell membrane capacitance measurements even though they were developed for different purposes. For example, scanning near-field microwave microscopy (SNMM) [4-7] is developed for thin film dielectric constant measurement [8]; scanning electrochemical microscope (SECM) [9, 10] and scanning ion-conductance microscope (SICM) [11-14] are developed for surface chemistry and surface topography examinations in liquid. However, these scanning approaches are inconvenient to use due to their needle-shaped electrodes. While SECM and SICM have low temporal resolutions due to their intrinsically slow measurement processes. As a result, these methods have not been reported for cell membrane capacitance measurement in liquid.

1.2 Sensors Inspired by Nanoscience and Nanotechnology

Nanoscience and nanotechnology refer to the research and application of structures or materials with at least one dimension of the order of less than 100 nm. Some structures and materials smaller than 100 nm usually have new properties and behaviors which are not presented by bulk status of the same composition. These new properties are caused by the specific phenomena that display new chemistry and physics of the particles. One of the most intuitive effects is due to the change in the surface/volume ratio [15]. When the size of the structure is decreased, the ratio increases and the surface phenomena predominate over the chemistry and physics in the bulk. Naturally, these new properties
associated with the small dimension are much more important than dimension itself. As a consequence, new sensors have been built to study and take advantage of nano materials. These sensors could be classified by different criteria. The most widely used are: sensors base on nanoparticles and nanoclusters, sensors based on nanowires and nanotubes, sensors base on nanostructures embedded in bulk materials, and sensors based on porous silicon.

The integration of microwave-based liquid sensing and nanofluidics has revealed an innovative approach as a sensing technique. Sensitivity, selectivity, and liquid volume could all be optimized comparing with traditional liquid detection techniques. Microwave-based liquid detection, also known as Electromagnetic sensing of liquid, can provide more detailed information of their molecular content such as polarizations, relaxation phenomena, interactions between molecules and so on [16]. And the challenge mainly resides in sensing and quantifying small contents of molecules, which is usually on nanoliter level, of cell suspensions, protein/DNA solutions, bacteria and pollutants. For sample manipulation and analysis purposes, extremely small nanofluidic channels need to be fabricated and used. A single nano-channel can be used to observe and detect individual molecules. Meanwhile, nano-channel arrays are also important to analyze sample heterogeneity which could possibly be averaged out in traditional population based arrays [17].

The critical issues for fabricating nano-channels are scaling down and packaging. Traditional photolithography based fabrication techniques cannot create sufficiently small sizes used in nonafluidics. And the channel enclosure is also a hot topic in nano-channel preparations. Various new techniques have come into place such as
nanoimprint lithography, electron beam lithography, and focused ion beam milling. These techniques vary in resolution, throughput and expense. For channel sealing, both traditional and innovative techniques are used such as wafer bonding and soft elastomer sealing.

1.3 Metal Thin Film Preparation

Since nanometer is such a magical size of common material that novel properties can only be revealed on this dimension level. Many efforts are made on developing and optimizing approaches for preparing different common materials on nanometer level, especially metals, which are extremely important in many different areas.

A variety of fabrication techniques have been developed to yield high quality metallic wires, rods, islands, and films on nanometer level. The thin film deposition techniques are commonly done by evaporation and sputtering. The analysis of the surfaces that are deposited by the listed methods reveals a rough topology – often rougher than the desired size of nanoscale structures [18]. This rough topology will decrease device reliability and sensitivity. It’s also considered as a major source of loss at optical frequencies. For these reasons, a smooth metal surface is an important prerequisite for many devices and systems in the future. Different approaches are tried to deal with this issue. Most methods are based on chemical and mechanical techniques such as polishing and pressing.
1.4 Studies on Malarial Pigments

Globally, numerous efforts are made to eliminate and prevent malaria in early stages. However, it’s still the most malignant vector-borne infectious disease with more than 200 million clinical cases and 1 million fatalities a year [19]. One of the most critical issues is the increasing drug resistance of the parasites. As a result, diagnose in early stage with cost-efficient methods and affordable vaccines are in highly demand for those malaria countries.

There are several methods currently used to diagnose malaria. Among them, microscopic observation of blood smears is the most powerful one. However, it’s quite expensive since it requires high-powered microscopes and critical test environment. Another commonly used method is antigen-based detection of malaria, which is more rapid and affordable. But it still has major drawbacks. One limitation is that this method is not sensitive enough for early-stage infections. Another is not being quantitative enough to distinguish between different levels of infections. Additionally, this method causes more errors. In the last several years, many new diagnostic approaches were brought up and developed in order to overcome the limitations of the traditional methods. Some of the new methods are still based on microscopic detection of infected cells. Meanwhile, more and more attention has been put to the methods using malarial pigments as the target material for magnetic diagnosis.
1.5 Outline of Thesis

In the following chapters, the fabrication and characterization of radio-frequency sensors designed for different purposes, including dielectric thin film detection, confined liquid detection, nano-channels realization, and EPR studies on malarial pigments, will be presented. Simulating results, measured results and preliminary conclusions will be discussed. And future work will also be planned as the final part of each chapter.
CHAPTER 2

PLANAR RF PROBES FOR THIN FILM DIELECTRIC PROPERTY IMAGING IN LIQUID

2.1 Introduction

An ultra-sensitive RF sensor was recently proposed and demonstrated for the measurement of minute dielectric property change [20]. Significant output signals (i.e. frequency shift and magnitude change of $|S_{21}|$) are observed when a single yeast cell passes through the sensor in liquid [21]. Therefore, the sensing mechanism can be exploited to measure cell membrane local capacitance in liquid and to address the limitations of those methods discussed in subsection 1.1. However, the uniform sensing transmission lines in [20, 21] do not provide high spatial resolutions. Hence, new techniques need to be developed to address this problem. In this chapter, we propose to use superstrate, which has a dielectric permittivity smaller than that of the substrate, to confine RF fields and use planar probing windows to provide localized probing fields. In the window, the high dielectric permittivity of liquid (i.e. water) enables strong RF fields. As a result, high 3D spatial resolutions can be achieved. Through simulation studies and experimental measurements with Duroid-board-based devices, we demonstrate the proposed techniques.

2.2 Planar RF Probe Design Considerations

Fig. 2.1(a) shows the proposed planar RF probe. It measures signal transmission coefficient ($S_{21}$), instead of reflection. The properties of materials-under-test (MUT) at
the probing window will be obtained from $S_{21}$. The interference process proposed in [20] is used to minimize common mode parasitic signals, which is essential for high-sensitivity sensing [7], especially in liquids [1]. Fig. 2.1(b) shows the incorporation of superstrate [22] into the coplanar waveguide (CPW) for field confinement. A probing window is opened for localized thin film detection and analysis. The window will be filled with water (solution) when the MUT is in liquid. Additional metal can also be deposited in the window to locally extend CPW signal electrode in z direction in order to further strengthen probing field. HFSS simulation results in Fig. 2.2(a) and (b) show that the superstrate does confine RF fields outside the probing window area even though partial leakage exists [22]; the water filled window has enhanced probing fields due to high dielectric permittivity. As Fig. 2.2 shows, when CPW is covered by superstrate, E-field on top of the superstrate is about $1.97 \times 10^7$ V/m. While for the same CPW, E-field is $7.63 \times 10^7$ V/m at the same height (z direction) but different planar position (x, and y direction), where there’s an opening and the signal line of CPW is exposed. E-field closely on top of the signal line inside the window could be as high as $1.8 \times 10^8$ V/m. Therefore, the dimensions of the window determine the lateral spatial resolutions (x and y directions) while field penetrations in z direction determine vertical spatial resolution. Hence, the proposed technique promises to achieve ultra high spatial resolutions when nanometer windows are obtained with advanced nanofabrication techniques, such as e-beam lithography.

Metal thin films can be deposited on top of superstrate to further improve RF field confinement results. Fig. 2.3(a) and (b) show field distributions at the probing window
and elsewhere when there’s a metal thin film on top of the substrate. Inside the sensing window (as Fig. 2.3(a) shows), E-field at the height of metal film/superstrate interface is $7.9 \times 10^7 - 1.2 \times 10^8$ V/m; when measuring point is at the height of the top metal surface but still inside the window, E-field is $7.1 \times 10^7$ V/m. When CPW is covered by substrate and metal film on top, no E-field is outside the window. It is clear that metal thin films are effective in field confinement. Hence, possible interference due to interactions between leaking RF fields and any sample components outside the probing window can be completely eliminated.

Fig. 2. 1 (a) Schematic of the proposed planar RF probe. (b) Illustration of the proposed RF probing window when coplanar wave guide is used to build the planar RF probe.
Fig. 2.2 Electric field distributions inside and outside the probing window. Superstrate is 100 nm thick. The signal line and gaps are 100 nm wide.

Fig. 2.3 Electric field distribution inside and outside the probing window, when a thin metal film is applied to help confine RF fields. The superstrate is 50 nm thick. The metal film is 100 nm thick. The signal line is 200 nm wide. Then gaps are 172 nm wide.
The sensitivity of the proposed planar RF probe is determined by the cancellation level of common mode signal in Fig. 2.1(a). Previous experimental results [20, 21] indicate that extremely high sensitivity, therefore, high-3D-spatial resolutions, can be achieved. Nevertheless, detailed and desired simulation analysis of the whole device in Fig. 2.1(a) is yet to be conducted since the device is multi-scale and requires significant computation power.

2.3 Measured Results

Rogers’ TMM3 boards are used to fabricate a simple CPW transmission line device, shown in Fig. 2.4(a), with Polydimethylsiloxane (PDMS) as a superstrate layer (0.67 mm-thick, \( \varepsilon_r = 2.5 \)) and a probing window on PDMS to demonstrate the field confinement effects and enhancement effects in Fig. 2.2. The CPW has a 2 mm signal line width (S in Fig. 2.1) and 142.16 \( \mu \)m gaps (W). The substrate thickness is 30 mil with \( \varepsilon_r = 3.27 \). Fig. 2.4(b) and (c) are the schematics of cross-section A and B in Fig. 2.4(a). Fig. 2.4(d) and (e) are the schematics of cross-section A, when water fills up the window, and when thin film sample is placed on the window with water in the window. These are the different situations we chose to conduct the experiments.
Fig. 2.4 (a) The RF sensor. (b) Schematic of cross-section A in (a). (c) Schematic of cross-section B in (a). (d) Schematic of cross-section A when water fills up the window. (e) Schematic of cross-section A when thin film sample is on top of the window and water inside the window.

An HP8510C vector network analyzer is used to measure the scattering parameters of the device after a full two-port calibration. Fig. 2.5(a) shows that $S_{21}$ is almost identical when different samples (1 cm $\times$ 1 cm squares, 0.5 mm thick) are placed on top of the PDMS superstrate layer, but outside the probing window. The results agree with those in Fig. 2.2 and indicate that PDMS is appropriate in confining RF fields outside the probing window. Fig. 2.5(b) shows that DI water (30 $\mu$L) in the probing window causes significant $S_{21}$ changes due to water high relative permittivity. It also shows that placing
the same TMM3 substrate material to cover the probing window causes significant $S_{21}$ change when there is water in the window. The differential increase from $\sim 0.2$ dB to $\sim 2$ dB as frequency increases. But no obvious change occurs when there is no water. Therefore, the change is due to the very part of TMM3 substrate that is over the window (i.e. a “voxel”) since the part that is outside the window does not cause obvious changes. Furthermore, the electric field within the probing window is effectively enhanced by water, which always appears when live cell membrane is to be probed.

Measurements with different samples, including mica, quartz, silicon, and Rogers’ TMM3 substrate, are also conducted with different thicknesses for multiple times. The results show clear $S_{21}$ dependence on both sample dielectric properties and sample thickness, which are the two properties we concern in the detection of cell membranes.

The above measurement results show that the measured $S_{21}$ carries the dielectric property information of the sample “voxel”, which is defined by the probing window and probing field penetration in $z$ direction. The signal of a “voxel” is usually very weak and difficult to measure with the simple CPW line when the “voxel” is small. Then the interference process in Fig. 2.1(a) will help capture minute $S_{21}$ changes to obtain material properties.
Fig. 2.5 (a) Measured transmission scattering parameters with samples outside the probing window. (b) Measured transmission scattering parameters for different test arrangements.
Fig. 2.6(a) shows the picture of a planar RF probe. Microstrip line, instead of CPW, is used to build the device with two purposes: (1) to demonstrate the functionality of the proposed techniques for thin film characterization in liquid, and (2) to show that other transmission lines, in addition to CPWs, can also be used to build the proposed device with new features. Since a microstrip line has its RF field concentrated between the signal strip conductor and the ground plane, we opened two probing windows, 4 mm × 4 mm squares aligned with the center of the two signal branches, on the ground plane while exploiting the ground plane to shield RF electric fields elsewhere. The measurement results are shown in Fig. 2.6(b). It shows that the minimum point of $S_{21}$ (cancellation) changes significantly when different materials are in the probing window. It should be pointed out that the RF probe is much more sensitive when small perturbations are involved [20], while the perturbation in Fig. 2.6 is large.
Fig. 2.6 (a) The fabricated RF sensor based on two Wilkinson power dividers with probing windows on the ground plane. (b) Measured $S_{21}$ magnitude with different materials in the probing window.

Due to current fabrication limitations, PDMS thin films and millimeter-sized windows are used in our experimental efforts to verify the proposed field confinement and probing window technique. The experimental process does not provide sufficient accuracy for quantitative data processing. The problem will be addressed in the future with the use of micro/nanofabrication techniques, which enable accurate control of
geometry, dimension and probing window alignment. Furthermore, when advanced nanofabrication techniques are used, the probing windows can be reduced to micrometer and nanometer levels. Dimension scaling indicates that the proposed superstrate and probing window approach are promising for nanometer 3D resolutions measurements [20, 21]. Fig. 2.7 shows some microscopic images of the sensor samples fabricated at Argonne National Lab. Fig. 2.7(a) and (b) are the sensing zone of a tapered CPW covered by SiO₂ superstrates. There’re openings at the center of the superstrates leaving CPW exposed to MUT. Fig. 2.7(c) and (d) are the images taken after metal thin films are deposited on top of superstrates. Multimeter is used to confirm that the metal layer is connected to the ground of CPW. The whole fabrication process is yet to be fully developed. And characterizations also need to be done. Nevertheless, this fabrication shows the potential of scaling down the proposed RF sensor in order to detect samples in smaller dimensions such as cells, particles, and molecules in the future. Another parameter of the probe is its temporal resolution, which is important for certain imaging applications (such as lipid rafts). For our proposed RF probes, the resolution is determined by electronic signal generation and detection, which can be as short as a few microseconds when a vector network analyzer is used.
Fig. 2.7 (a) 50 μm × 50 μm SiO₂ superstrate on top of a CPW with a 20 μm × 20 μm window at the center. (b) 20 μm × 20 μm SiO₂ superstrate on top of a CPW with a 5 μm × 5 μm window at the center. (c) Superstrate covered by 50 nm Chromium and 10 nm Gold. (d) Superstrate covered by 50 nm Chromium and 50 nm Gold.

2.4 Conclusions

In summary, we propose a planar RF probe to measure the dielectric properties of thin films in liquid at high spatial and temporal resolutions. We use a previously demonstrated interference method to provide probe sensitivities to measure materials in a small “voxel”. Superstrate is proposed for RF field confinement while probing widows
are used for local dielectric material detection and analysis. Both techniques are demonstrated through HFSS simulations and experimental measurements with prototype devices, in addition to a microstrip line based planar RF probe demonstration. Future work includes demonstrating the techniques quantitatively with nanometer spatial resolutions, understanding the limitations of the proposed technique, and conducting cell membrane measurements.
CHAPTER 3

COPLANAR WAVEGUIDES WITH SUB-10 NM GOLD FILMS

3.1 Introduction

Broadband dielectric spectroscopy is an emerging technique for label-free and non-invasive detection and analysis of molecules and cells in aqueous solutions [23, 24], for which transmission lines and metallic electrodes are incorporated with microfluidic channels. Yet broadband dielectric spectroscopy has not been implemented with sub-10 nm fluidic channels, which have been developed for the study of confined DNA molecules and confined water, in addition to many other substances and processes. Optical observations and DC measurements have been the main approaches for these investigations. The former needs fluorescent labeling while the latter only provides limited information contents. Integrating transmission lines with sub-10 nm fluidic channels can provide the missing dielectric spectroscopy capabilities and address these issues.

However, such integration is very challenging since building reliable and controllable sub-10 nm channels is a major challenge by itself despite various efforts, including nanolithography [25], nanoglassblowing [26], nanoimprint lithography [27], and polysilsesquioxane sealing [28]. The native oxide etching (NOE) [29] approach has issues on silicon contact and silicon transmission line dispersion. A potential new approach is to develop sub-10 nm transmission lines, such as the coplanar waveguides (CPWs) in this work, and wafer bonding techniques, as shown in Fig. 3.1(a).
Nevertheless, sub-10 nm transmission lines, including CPWs, have not been reported so far despite the fact that thin film CPWs are also of great interest in many other applications, such as high-speed interconnect [30] and high-sensitivity sensors [31, 32].

For sub-10 nm CPWs, their metal thickness is much smaller than the electron mean-free paths (MFP) in bulk metal [30-33], such as gold (MFP ~ 30 nm) in this work. The thickness is also comparable to the reported percolation threshold of gold (~ 8 nm), below which gold thin films are arrays of disconnected islands [34]. As a result, electron conduction processes are much different from those in thick film CPWs [35]. For instance, electron scatterings at gold film surfaces and grain-boundaries become dominant factors. Surface roughness effects are likely to be more pronounced while skin effects are insignificant. These size effects [36] have attracted great interest, but at DC [37], terahertz (THz) [38] and optical frequencies [39], not much in microwave frequencies.

In this chapter, we report our preliminary results on techniques of building sub-10 nm CPWs and present their equivalent circuit parameters up to 40GHz.
3.2 Fabricating Sub-10 nm CPWs and AFM Inspection

Building sub-10 nm ultra-smooth metal thin film is an interesting topic in nano-scale material technology. As discussed in subsection 1.3, metal thin films are commonly deposited by evaporation and sputter, which generate quite rough surfaces. Therefore efforts have been made on developing chemical and mechanical processes to smooth out the deposited surface. In our fabrication process, we applied a pressing technique to upgrade the gold thin film surface morphology, and furthermore, to improve the device’s electrical properties. In the following subsection, the fabrication steps are demonstrated in details, including both standard protocols and process developments for our specific considerations.
3.2.1 Fabrication Steps

Our CPW layout is shown in Fig. 3.1(b), which has 100 μm width (S) and different signal-ground gaps (H) ranging from 5 μm to 20 μm. Standard lithography and lift-off processes are used to deposit gold films on fused silica wafers, which have less than 1 nm root-mean-square (RMS) surface roughness. The fused silica substrates are 4” in diameter and 500 μm in thickness, purchased from University Wafers. In standard fabrication process, the first thing to do with fresh substrates is cleaning, in order to make sure there’s no dust, particles, organic material on the wafer surface. In clean room, the Hamatech Hot Pirannha tool was used to do the high quality cleaning on the wafers. Photolithography was processed to transfer patterns onto substrates. Firstly, we used YES Vapor Prime Oven to do the HMDS priming on the substrates. This process is necessary because it can improve the adhesion of photoresist on the substrates, which will generate accurate patterns with good precision especially when the critical feature is comparatively small (2 μm-5 μm). The second step is spin-coating photoresist on the primed substrates. The photoresist we used was Shipley 1813 positive photoresist, which works well for liftoff process. The photoresist was span at the speed of 3000 rpm with an acceleration of 1000 rpm for 60 seconds. Then the substrates were baked at 115°C for 60 seconds. The third step is UV-exposing. Suss MA6-BA6 Contact Aligner was applied to expose the coated and baked substrates for 5.8 seconds for this specific photoresist and thickness. The photo mask was written and etched by Heidelberg Mask Writer DWL2000 and Hamatech-Steag Mask Processer. After exposing, the substrates were developed in 726 MIF water developer for 60 seconds, then rinsed and dried properly. After
photolithography was finished, oxygen descum should be processed. This procedure can make the exposed substrate surface clean enough for any succeeding steps such as metalization. This step was done by Oxford 81 Etcher with a standard Oxygen Clean Recipe for 30 seconds. E-beam evaporation was processed by CVC SC4500 E-gun Evaporation System. The evaporation rate was inspected by crystal monitor installed in the system and had an effect on the surface grain size. There’s another issue associated with evaporation rate. The deposited metal thickness is calculated by the system. But the starting and finishing point is controlled manually. As a consequence, an error could be introduced here. When depositing thin layers with critical thicknesses (not surface roughness), slower evaporation is recommended to provide a better control and avoid a substantial thickness error. After metal deposition, substrates were dipped into 1165 photoresist remover for overnight liftoff. If there was any residue that cannot be washed away after liftoff, sonication hot bath could be used for a thorough liftoff.

3.2.2 Atomic Force Microscopic Measurements of Surface Morphology

The surface morphology of newly deposited gold thin film was inspected by Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM). For SEM, since the thin film has a thickness smaller than 10 nm, which is not thick and conductive enough to scan as standard SEM samples, the resolution cannot be optimized and the contrast was below normal inspection requirement, as shown in Fig. 3.2. In this case, AFM is a better choice to see the details of the surface morphology clearly, especially when we need to compare small difference of pressed and un-pressed surface in the next subsection.
AFM measurement results indicate that different deposition conditions generate different surface morphologies. Here are some examples. Fig. 3.3 and 3.4 show the difference of the thin films evaporated at low and high rates. Both samples are deposited by 2 nm titanium and 5 nm gold. The evaporation rate of titanium is 1 \( \lambda /s \) for both. But the evaporation rates of gold are 0.4 \( \lambda /s \) and 3 \( \lambda /s \) respectively. From these images, we can conclude that higher evaporation speed will generate smaller height variation in a local area, and the surface is smoother than those evaporated at lower rate. There’re only a few data about the relationship between evaporation rate and deposited surface morphology. Rosenhain and Ewen found that the rates of evaporation of polystalline silver, copper, and zinc increase appreciably with decrease in grain size [40]. And smaller grain size gives smoother surface. Lee, Hsueh, etc also discovered that slower deposition
rate resulted in approximately a 6-fold increase in the average surface-grain size on both silicon and glass substrates [41].

A layer of titanium is necessary for adhesion purposes. For our samples, we deposited 2 nm of titanium before evaporating gold. In order to see whether titanium has any effect on the final gold surface morphology, we compared this sample with a reference sample deposited by only 7 nm thick gold at the rate of 3 Å/s, shown in Fig. 3.5. As expected, the 2 nm titanium is a uniform thin film and can slightly improve the surface roughness of gold layer. The heights of these 7 nm thick films are also measure, as Fig. 3.6 shows. There’re some spurs due to the deposition and liftoff process which were avoided when measuring the surface morphology.

Fig. 3.3 AFM image of the surface morphology with height indication of gold thin film deposited at 0.4 Å/s (2 nm titanium is deposited as adhesion layer).
Fig. 3.4 AFM image of the surface morphology with height indication of gold thin film deposited at 3 \( \lambda \)/s (2 nm titanium is deposited as adhesion layer).

Fig. 3.5 AFM image of the surface morphology with height indication of gold thin film deposited at 3 \( \lambda \)/s (no titanium is deposited).
3.2.3 Smoothing Gold Thin Film Surface by Mechanical Pressing

In order to obtain even smoother gold surface, we used mechanical presses, shown in Fig. 3.7, to apply a pressure of about 100 MPa to 150 MPa on our gold thin film samples. The improvement of the surface morphology by this pressing process is also inspected by AFM. From Fig. 3.8, we can easily observe that the pressed gold surface has negligible height variation which tells the fact that the film is uniform and smooth.
Fig. 3.7 Mechanical presses used for smoothing gold thin film surface.

Fig. 3.8 AFM image of the surface morphology with height indication of gold thin film deposited at $3 \text{ } \lambda /s$ (2 nm titanium is deposited as adhesion layer) after surface deformation (pressed by 150 MPa).
3.3 Electrical Parameters of Sub-10 nm CPWs

3.3.1 DC Resistance

Table I lists the measured DC resistance of 3 CPWs, which are 100 μm wide. It shows that the pressed-7 nm CPW has much smaller resistance compared with the un-pressed CPW due to smoother and more continuous gold films. Table I also shows that DC currents affect film resistance values significantly, which indicates strong effects of DC voltages on thin film conductions as discussed in [42]. At high-currents, the pressed and un-pressed films have similar resistance. Nevertheless, the calculated resistivity of 7 nm CPW at 50 mA current is \( \sim 3.57 \times 10^6 \) S/m, about 10 times worse than that of bulk gold, \( 4.10 \times 10^7 \) S/m. Electron scatterings at film surface and grain boundaries are the main sources of high resistivity.

When 2 nm titanium is deposited before gold, the resistance is much smaller because titanium forms a relatively uniform and conductive layer even when it’s very thin. Table II shows the DC resistance of samples with different gold thicknesses. It indicates that resistance is smaller for thicker films and less dependent on DC current.
Table I: A comparison of gold thin film CPW resistance.

<table>
<thead>
<tr>
<th>DC Currents</th>
<th>8-nm-CPW (1 mm long)</th>
<th>7-nm-CPW (7 mm, not-pressed)</th>
<th>7-nm-CPW (7 mm, pressed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 μA</td>
<td>N/A</td>
<td>7.92 MΩ</td>
<td>575 kΩ</td>
</tr>
<tr>
<td>10 μA</td>
<td>17.64 kΩ</td>
<td>1.14 MΩ</td>
<td>80.05 kΩ</td>
</tr>
<tr>
<td>100 μA</td>
<td>3.447 kΩ</td>
<td>202.7 kΩ</td>
<td>50 kΩ</td>
</tr>
<tr>
<td>1 mA</td>
<td>1.754 kΩ</td>
<td>58.5 kΩ</td>
<td>23.37 kΩ</td>
</tr>
<tr>
<td>5 mA</td>
<td>1.655 kΩ</td>
<td>18.28 kΩ</td>
<td>14.63 kΩ</td>
</tr>
<tr>
<td>10 mA</td>
<td>N/A</td>
<td>8.64 kΩ</td>
<td>7.24 kΩ</td>
</tr>
<tr>
<td>20 mA</td>
<td></td>
<td>4.22 kΩ</td>
<td>3.03 kΩ</td>
</tr>
<tr>
<td>50 mA</td>
<td></td>
<td>1.30 kΩ</td>
<td>1.4 kΩ</td>
</tr>
</tbody>
</table>

Table II: A comparison of gold thin film CPW resistance (for different thicknesses).

<table>
<thead>
<tr>
<th>DC Currents</th>
<th>2 nm Ti + 4 nm Au</th>
<th>2 nm Ti + 6 nm Au</th>
<th>2 nm Ti + 8 nm Au</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22.42 kΩ</td>
<td>15.86 kΩ</td>
<td>3.703 kΩ</td>
</tr>
<tr>
<td>1 μA</td>
<td>19.85 kΩ</td>
<td>2.185 kΩ</td>
<td>1.399 kΩ</td>
</tr>
<tr>
<td>5 μA</td>
<td>20.13 kΩ</td>
<td>2.184 kΩ</td>
<td>1.399 kΩ</td>
</tr>
<tr>
<td>10 μA</td>
<td>20.11 kΩ</td>
<td>2.181 kΩ</td>
<td>1.38 kΩ</td>
</tr>
<tr>
<td>50 μA</td>
<td>20.09 kΩ</td>
<td>2.171 kΩ</td>
<td>1.38 kΩ</td>
</tr>
<tr>
<td>100 μA</td>
<td>20.07 kΩ</td>
<td>2.155 kΩ</td>
<td>1.38 kΩ</td>
</tr>
<tr>
<td>500 μA</td>
<td>20.04 kΩ</td>
<td>1.987 kΩ</td>
<td>1.38 kΩ</td>
</tr>
</tbody>
</table>
3.3.2 High-frequency Equivalent Circuit Parameters

The method in [43] is followed to obtain 8-nm CPW equivalent circuit components, i.e. $R$, $L$, $C$, and $G$ from scattering parameters. The results of $R$ and $L$ are shown in Fig. 3.9. A few observations can be made. First, at low frequencies, $R$ stays relatively unchanged and its value decreases at high frequencies. This further indicates that the 8 nm thickness is likely around the percolation threshold, where continuous metal thin films begin to form. Nevertheless, capacitive couplings between gold islands play an important role in transmitting signals. Similar phenomena have been observed at MHz frequencies when measured with 4-point approaches [44]. Secondly, CPW inductance, $L$, is also orders of magnitude higher than that of conventional CPWs. The higher inductance at low frequencies is caused by long and meandered current paths that connect metal islands. Thirdly, the capacitance between signal line and ground, $C$ (not shown), is smaller than that of thick film CPWs. This indicates that the actual distance between signal trace and ground (return path) is larger than the gap $H$ in Fig. 3.1(a). As a result, the characteristic impedance $(L/C)^{1/2} \approx 200 \, \Omega$ is very high in this frequency region.

Fig. 3.10 compares the measured $S_{21}$ magnitude of 7 nm CPWs at two different DC currents. It is shown that (i) below $\sim 15$ GHz, $S_{21}$ magnitude decreases with frequency, as anticipated, (ii) the CPWs have low $S_{21}$ magnitudes around 15 GHz, which corresponds to $\sim \lambda/2$ of the CPWs, (iii) above 15 GHz, $S_{21}$ magnitude flattens out, and (iv) DC current improves $S21$ magnitude significantly due to improved conductivity.
Fig. 3.9 Measured 100 μm wide 8 nm CPW resistance R (a) and inductance L (b).

Fig. 3.10 S-parameters of 7 nm CPWs before and after surface deformation at two DC currents.
Fig. 3.11 shows the R and L parameters of the obtained 7 nm CPWs when the applied DC current is 1 mA. A few observations can be made. First, pressure-induced surface deformation causes significant RF property changes. Without the deformation process, the obtained CPW parameters are very noisy (Fig. 3.11(a)), probably due to frequency dependent conduction paths and thermal noise background. Second, the pressed 7-nm CPW has much different R and L parameters compared with 8 nm CPW in Fig. 3.9. Its R is more than 10 times smaller than that of 8 nm CPW even though it is thinner. Its R also does not decrease with frequency, indicating that the film thickness is above the percolation threshold of such films. The inductance in Fig. 3.11(b) is much smaller than that in Fig. 3.9(b), further indicating the lack of meandered current paths. As a result, the impedance (~ 50 Ω) of the 7 nm CPW is much smaller than that of the 8 nm CPW. At low frequencies, 7 nm CPW has larger L & C variations vs. frequency. This indicates there still are frequency dependent current paths. Further surface deformation at higher pressures (> 150 MPa) could help address this issue. In Fig. 3.11(b), L decreases at high frequencies. This is likely caused by current redistributions that would occur even for perfect continuous metal films. Finally, the conventional skin effect is not a major concern here, as shown in Fig. 3.11(a).
Fig. 3.11 The extracted R (a) and L (b) of 7 nm CPW. The L of un-pressed 7 nm CPW is not shown.

When a 2-nm thick titanium layer is deposited first and the total thickness of CPW increases to 8 nm (2 nm titanium and 6 nm gold) and 10nm (2 nm titanium and 8 nm gold), a more uniform metal layer is formed. The CPW’s transmission is also improved as Fig. 3.12 shows. Furthermore, pressing process also works well in this case to generate more continuous and smooth gold layer. Thus the S$_{21}$ of the pressed sample is even better.
The R, L, C, and G extracted from S-parameters of these listed conditions are shown in Fig. 3.13 for 8 nm CPW (2 nm titanium and 6 nm gold) and Fig. 3.14 for 10 nm CPW (2 nm titanium and 8 nm gold). For both thicknesses, pressed CPW has a smaller R than the un-pressed one, which, once again, reflects the fact that the gold thin film surface has been smoothen out through the pressing techniques.

The difference in $S_{21}$ of different thicknesses is compared in Fig. 3.15. The three $S_{21}$ curves correspond to 2 nm Ti + 4 nm Au, 2 nm Ti + 6 nm Au, and 2 nm Ti + 8 nm Au, respectively. All of the above CPWs have the length of 7 mm, which is decided by the fabrication and characterization environment since they finally will be used as the bottom compartment of the nano-channel devices. In order to inspect the difference in thin film CPWs with different lengths, we also compared the S-parameters in broadband of 2 mm and 7 mm long CPWs. Fig. 3.16 shows the results. As expected, the shorter CPWs have better transmission than the longer ones.
Fig. 3.12 (a) S-parameters of 8 nm (2 nm Ti + 6 nm Au) CPWs before and after surface deformation. (b) S-parameters of 10 nm (2 nm Ti + 8 nm Au) CPWs before and after surface deformation.
Fig. 3.13 R (a), L (b), C (c), and G (d) of 8 nm thick CPWs before and after pressing.
Fig. 3.14 R (a), L (b), C (c), and G (d) of 10 nm thick CPWs before and after pressing.

Fig. 3.15 S-parameters of CPWs with different thicknesses before surface deformation.
Fig. 3.16 S-parameters of 6 nm CPW (2 nm Ti + 4 nm Au) (a), 8 nm CPW (2 nm Ti + 6 nm Au) (b) and 8 nm CPW (2 nm Ti + 6 nm Au) (c), with difference lengths.
3.4 Conclusions

CPWs, made of 6, 7, 8, and 10 nm thick metal films, are fabricated and characterized. The AFM images and experimental results show that deposition conditions have certain effects on gold surface roughness. And pressure-induced surface deformation techniques can improve the surface roughness significantly. Sub-10 nm CPWs have large resistance and loss with small dispersion when compared with thick metal CPWs. Thus, such CPWs are better suited for applications where line length is short, such as nanofluidic channels.
CHAPTER 4

NANO-CHANNELS BASED ON THIN FILM CPWS

FOR STUDY ON CONFINED LIQUID

4.1 Introduction

Scaling down from microfluidics to nanofluidics is a requirement of the synthesis, manipulation, and analysis of various materials on molecular level (1-10nm). The availability of nanofluidic tools, which have the dimensions close to or smaller than target biomolecules and organelles already has made great contribution to biochemical and biomedical science and keeps growing. In addition to the application to these areas, nanofluidic tools are also significant to chemistry and physics studies because promising new phenomena are discovered, which have never been observed on micro or macro level [15].

As discussed in Chapter 3, our ultimate goal is the implementation of nonafluidic channels and the characterization of confined liquid materials. Despite the various methods currently in use, we adopt a new approach using thin film transmission lines as basic structures of the nano-channels. In this chapter, the fabrication and characterization of the nano-channels we built based on the thin film CPWs introduced in Chapter 3 will be illustrated.
4.2 Fabrication Process of Nano-channels

The nano-channels are achieved by bonding a bottom wafer with thin film CPWs to a top wafer with sample handling functionalities. The layouts of individual devices are illustrated in Fig. 4.1. In these figures, red areas refer to 7 mm × 6 mm gold thin film CPWs bonded with fused silica. Purple areas represent through holes on the top wafer. Green areas are trenches on the bottom side of the top wafer. Fig. 4.1(a) and (b) show two types of nano-channels we fabricated and characterized. The main difference between them is the presence of a well (for containing MUT) covering signal line and signal-ground gaps in the sensing region of the second type.

![Image](image_url)

Fig. 4.1 (a) The first type of nano-channels without a center MUT well. (b) The second type of nano-channels with a center MUT well.
The fabrication process of the bottom wafer is discussed in Chapter 3. The fabrication of the top wafers is much more complicated where several more equipments and tools are involved. Because the whole process is neither standard nor commonly used, great efforts were made on process development. And a doable routine was finally brought up.

The top wafer substrates are still 4” fused silica wafers. Since we need to make electrical connection to the CPW ports on the bottom wafer, there should be some through holes in the top wafers big enough to expose the gold pads and let the probe tips touch town. Similar through holes are also needed as the inlets and outlets to make fluidic samples flow into the nano-channels. We used Versalaser Cutting/Engraving Tool to drill the through holes on fused silica by laser beam. After laser drill, there were many particles re-fused around the edges of each hole, looking like spurs and ridges with a height of about 30 to 50 μm. These ridges would cause trouble in wafer bonding since they may crack the bottom wafer when high pressure is applied. Even if the bottom wafer is not broken, both wafers are still not likely to bond to each other because the ridges hinder the interfaces from contacting completely. In order to remove the undesired ridges, we did chemical mechanical polishing by Strasbaugh 6EC CMP tool. The resulting surface profile showed that, after polishing, the ridges height was reduced to < 1 μm, which would not be a problem for wafer bonding process.

As the Fig. 4.1 shows, there should be some trenches on the bottom side of the top wafer, which were done by photolithography and wet-etching after drilling through holes and polishing. An alternative way is to etch these trenches before polishing out the edges.
CMP process will polish the substrate surface along with the ridges but at a lower rate. Therefore, if etching is prior to polishing, we need to consider how much the wafer surface will be polished when deciding the etching depth. Photolithography process is similar to the previous description except that here we used SPR 220-3.0 instead of the S-series photoresist simply because SPR has better adhesion on substrates and is preferable for etching process. SPR photoresist requires post exposure baking for 90 seconds at 115°C. Next step is to develop the substrate in 726MIF water developer for 3 minutes. BOE (buffered oxide etch) 6:1 was used to etch the trenches. The etching rate of this etchant is about 90 nm/min. Since the pattern we designed on the bottom surface of the top wafer is simply for holding incoming samples, the actual size is not critical here. Thus the undercut caused by the isotropic wet-etching could be ignored. Wet-etching is preferred to dry-etching because dry-etching may generate rough surface morphology on fused silica substrates when polymer or particles are deposited on the surface after etching. This could cause potential problems for wafer bonding. After etching, the substrates were dipped into 1165 to remove the photoresist.

One of the most critical issues for wafer bonding is surface cleanliness. Before bonding, the wafers were dipped into Nanostrip for 20 minutes to remove all the photoresist residue, organic solvent residue, particles and dust. Nanostrip is a harsh chemical that can easily remove the gold films on the bottom wafer if they’re not well adhered. This is the main reason why we decided to deposit 2 nm titanium prior to gold as the adhesion layer. After cleaning, both wafers were treated in oxygen plasma for 60 seconds to enhance the surface glutinosity. Then they were directly sent into Suss SB8e
Substrate Bonder for wafer bonding process. The bonding process should be done right after cleaning, because the longer the wafers are stored, the more dust and particles will be accumulated on the surfaces. The patterns on both wafers have a sufficiently large outline. Thus, rough alignment under microscope was sufficient. More accurate alignment is available by the Suss MA6-BA6 Contact Aligner tool, if needed. The bonding type was Thermo-Compression and the whole bonding process lasted for about 5 hours. Fused silica is easy to break or crack if the temperature and pressure goes up or down too fast. Therefore, it’s necessary to use a longer ramping time to increase and decrease environment change slowly. The applied temperature was 330° C and pressure was 6000 mbar.

The final device is shown in Fig. 4.2. Microscopic images in Fig. 4.3 show the connecting section of the nano-channels on the bottom wafer and trenches on the top wafer.

Fig. 4.2 An individual nano-channel device.
4.3 Simulation Setup and Results

A series of simulation was conducted via Ansoft HFSS to examine the high frequency broadband properties of the nano-channels qualitatively. Layouts are shown in Fig. 4.4. The signal line and gap widths are 100 μm and 15 μm respectively, which reflect the actual dimensions of the real devices. The CPW length is scaled down to 300 μm considering the simulation efficiency and PC’s computational capability. Metal thickness
is 30 nm to match the devices we used for measurement in the next subsection. Fig. 4.4(a) and (b) simulate two types of devices we designed and fabricated. Two times of simulations were run for each structure: without water and with water filling in the nano-channels (and the well in the second type). Fig. 4.5 shows the simulation results of $S_{21}$, where Fig. 4.5(a) is the $S_{21}$ magnitude comparison of the first type of device with and without DI water filling in the nano-channels. And Fig. 4.5(b) is the $S_{21}$ magnitude comparison of the second type of device with and without DI water. From the scattering parameters we get by simulating the 300 μm long devices, we can calculate those of the nano-channels scaled up to 7 mm long, in order to compare with the measured results in the next subsection. The scale-up $S_{21}$ magnitude comparisons are shown in Fig. 4.6.

Fig. 4.4 (a) The first type of nano-channels. (b) The second type with a well at the center.
Fig. 4.5. Simulating results of $S_{21}$ magnitude. (a) Comparison of the first type of device without and with water filling in the nano-channels. (b) Comparison of the second type of device without and with water filling in the nano-channels and the well.
Fig. 4.6 Calculating results of $S_{21}$ magnitude when the length of the device is scaled up to 7 mm. (a) and (b) correspond to devices describe in Fig. 4.4 (a) and (b) respectively.
4.4 Experimental Results

CPWs with different thicknesses are fabricated and tested to bond with the top wafers via Thermo-Compression Bonding, which is discussed in subsection 4.2. The bonding results showed that thinner metal films are not strong enough for this type of bonding. Nevertheless, when the gold film thickness reaches 30 nm with 5 nm thick titanium film as adhesion layers on both top and bottom interfaces to fused silica substrates, the bonding works well and it’s possible for water to flow inside the nano-channels without major leakage. In our measurement, we used these nano-channels to test DI water on probe station. The $S_{21}$ magnitude comparisons of the same device with and without water in nano-channels are shown in Fig. 4.7. Fig. 4.7(a) and (b) correspond to the two types of nano-channels in Fig. 4.1 (a) and (b). The measured results match the scaled-up simulation results well with reasonable errors and loss. Both simulation and experimental results indicate that the $S_{21}$ change is significant when there’s water in the channels, even though water is confined to nanoliter level, which cannot be easily detected by other methods because of its extremely small amount. R, L, C, and G of the two types of devices with/without water filling in the nano-channels (and wells) are extracted and shown in Fig. 4.8 and Fig. 4.9.
Fig. 4.7 Measured results of $S_{21}$ magnitude. (a) Comparison of the first type of device without and with water filling in the nano-channels. (b) Comparison of the second type of device without and with water filling in the nano-channels and the well.
Fig. 4.8 Extracted R (a), L (b), C (c), and G (d) comparisons of the first type of device with and without water filling the nano-channels.
Fig. 4.9 Extracted R (a), L (b), C (c), and G (d) comparison of the second type of device with and without water filling in the nano-channels and the well.

4.5 Conclusions

Nano-channels are realized by 40 nm thick CPW deposited on fused silica and bonded with another wafer. Simulations and characterizations are conducted showing the results matching each other well. At this moment, de-embedding and quantification are not available. Nonetheless, the preliminary fabrication and measurements show great potential in this approach to obtain more detailed information of confined liquids on
nanoliter level by measuring and analyzing scattering parameters of the CPW-incorporated nano-channels.
CHAPTER 5

DETECTION OF HEMOZOIN (MALARIAL PIGMENT)

ON RED BLOOD CELLS BY RF SENSORS

5.1 Introduction

Hemozoin, also known as malarial pigment, is a byproduct of the disease formed during the intraerythrocytic growth cycle of the parasites [45, 46]. Digestion of the hemoglobin by the malaria parasites results in the accumulation of monomeric heme. Heme then is transformed into an insoluble crystallized form. This process is accompanied by changing the valency and the local coordination of iron [19]. The low-spin diamagnetic Fe$^{2+}$ ions are transformed into high-spin paramagnetic Fe$^{3+}$ ions in hemozoin. This is the reason why magnetic diagnosis becomes possible to detect hemozoin. Apart from the diagnostic technique, hemozoin is also a main drug target and may act as an immune modulator as well [47, 48].

Hemozoin is chemically, spectroscopically, and crystallographically identical and isostructural to its synthetic phase, β-hematin [50]. There is a single high-spin (S=5/2) iron environment of largely axial symmetry in bulk phase, which has been proved by magnetic susceptibility measurements and Mossbauer spectroscopy on β-hematin [51, 52]. Multi-frequency high-field electron paramagnetic resonance (EPR) study on the malaria pigments has also obtained meaningful results including the definite conclusions of the spin state and properties of the ground state of hemozoin and β-hematin [50]. In this chapter, a new method of characterizing hemozin by EPR is proposed. Radio-frequency
sensors are used to capture the resonance of hemozoin on malaria infected red blood cells in magnetic field. Qualitative conclusions are drawn from the simulating and measured results of healthy and infected red blood cells.

5.2 Sensor Fabrication and Experiment Setup

5.2.1 Design and Fabrication of RF Sensors

Two types of microstrip-line-based sensors were fabricated for hemozoin detection. The layouts are shown in Fig. 5.1. Fig. 5.1(a) is a simple straight microstrip line with a 100 µm wide tapered section at the center. In order to increase the interacting surfaces within a confined area and volume, a structure improved by using meandered microstrip lines at sensing zone, as Fig. 5.1(b) shows, was also fabricated. The magnetic field distribution of this structure is shown in Fig. 5.2, which is a cross-section view of the meandered sensing zone. The substrate we used for the first sensor in Fig. 5.1(a) is still fused silica. They’re 1” × 3” slides with a thickness of 1 mm (purchase from AdValue Technology). This type of sensor was fabricated under clean room environment. Procedures such as substrate cleaning, photolithography, metal deposition, oxygen descum, and liftoff, were involved. Three layers of metal were deposited: 10 nm titanium (adhesion layer), 500 nm copper, and 100 nm gold (finishing layer for protecting copper from oxidization). Both top and bottom sides of the substrates are deposited by the same metal composition to form signal line and ground. After metalization, conductive e-poxy was applied to glue the connectors onto the ports of the sensor. We didn’t choose soldering, because the surface metal of the sensors is gold, which is not a commonly used metal to solder and tends to leave an insecure connection. Conductive epoxy has better
mechanical strength and electrical conductivity comparing with soldering, which helped build more reliable sensors. The second structure was fabricated on a planar circuit board by milling machine. Connectors were easily soldered on the ports in this case. PDMS was used to make the wells for holding MUT inside sensing zone. PDMS could be sealed on fused silica with excellent adhesion after being treated by oxygen plasma for one minute. On the contrary, the adhesion of PDMS on PCB substrate was not ideal. Thus, epoxy was needed to achieve reliable sealing. The final devices are shown in Fig. 5.3.

![Fig. 5.1](image)

(a)

(b)

Fig. 5.1 (a) Layout of the first type of microstrip lines with tapered 100 μm wide signal line at the center. (b) Layout of the second type of microstrip lines with meander lines at the center.
Fig. 5.2 Magnetic field distribution of the meandered microstrip line sensing section.

Fig. 5.3 (a) The first type of sensors. (b) The second type of sensors.
5.2.2 Measurement Setup

For this measurement, we apply the interference process similar to what we use in Chapter 2 and some of our group’s previous works [20, 21]. The improvement we make on this system is that external power-dividers are introduced to replace the Wilkinson power-dividers built directly on chip (circuit boards, wafers, and other substrates). This method eliminates the fabrication imperfections on power-dividers and provides more evenly-split RF signals. We also use tunable phase shifters and attenuators to have a better control of the phase and attenuation in both branches. The goal is to optimize the cancellation level. With these external components inserted into the system, shown in Fig. 5.4, now it’s relatively simple to obtain a cancellation level of about -100 dB with acceptable stability.

![The optimized systems of interference process with external power dividers, phase shifters, and attenuators (magnetic coils are not shown).](image)

Fig. 5.4 The optimized systems of interference process with external power dividers, phase shifters, and attenuators (magnetic coils are not shown).
Fig. 5.5 shows the coils we use to generate magnetic field. When measuring, they are connected in series to a current source. And the RF sensor with MUT is inserted between these two compartments. The relationship of input current and generated magnetic field is approximately linear as Fig. 5.6 shows. This is measured by a magnetic field meter with the sensing tip placed at the center of the coils, where samples will be placed for measurement.

Fig. 5.5 Coils for generating magnetic field.

![Coils for generating magnetic field](image)

![Input current vs Magnetic field graph](image)

Fig. 5.6 The generated magnetic field as a function of input current.
5.3 Measured Results

The infected and healthy red blood cells are prepared by Dr. David Peterson’s group at the University of Georgia. The buffer solution is phosphate buffered saline (PBS). Healthy red blood cell sample has an original concentration of 164 million cells/mL. Infected cell sample has an original concentration of 5 million cells/mL and a parasitemia of 80.3%. The microscopic image of infected cells is shown in Fig. 5.7, where the dark blue pigments are our targets, hemozoin.

Fig. 5.7 Microscopic image of the infected red blood cells.

Calibrated Vector Network Analyzer is used to measure the S-parameters of the interference system (mechanism is illustrated in [20] and [21]) with the sensor connected to the material branch, and sample covering the sensing zone. For the first type of sensors, sensing zone is comparatively small and only 20 μL of sample is needed. The sample volume increases to 150 μL when using the second type. Healthy red blood cells are
diluted to the same concentration level of the infected cells when using the first type of sensors. According to Sienkiewicz and colleagues’ High-field EPR measurement results [49], we calculate the resonant RF frequency for the magnetic field provided by our magnetic coils and tune around this frequency range. The current is increased gradually and the S-parameters are recorded corresponding to each current level (magnetic field). Each group of measurements is taken for multiple times to confirm repeatable and reliable measured results.

First we sweep the magnetic field in the whole available range, from 0 to 400 G (current: 0-1 A, step size: 0.1 A). Several observations are made. Firstly, center frequency of the signal cancellation curve shifts as the current (magnetic field) changes for both healthy and infected red blood cells. But the shift directions are opposite. Fig. 5.8(a) and 5.9(a) show that, when measuring healthy red blood cells, center frequency is shifting to lower value as the magnetic field increases. Nevertheless, when measuring infected ones, center frequency shifts to higher value as magnetic field increases, shown in Fig. 5.8(b) and 5.9(b). Secondly, the steps and total range of center frequency shift are related to the volume of solution and cell population. More cells under test can generate larger frequency shift. In other words, larger amount of samples are easier to detect. Thirdly, the magnitude of signal cancellation point is changing almost in the same way for both healthy and infected cells: as magnetic field increases from 0 to 400, the $S_{21}$ magnitude of the cancellation signal first drops and then goes back up gradually.
Fig. 5.8 $S_{21}$ of the interference system, when sweeping in the whole magnetic field range.

(a) Healthy red blood cells measured by the first type of sensors. (b) Infected red blood cells (with hemozoin) measured by the first type sensors.
Fig. 5.9 $S_{21}$ of the interference system, when sweeping in the whole magnetic field range.

(a) Healthy red blood cells measured by the second type of sensors. (b) Infected red blood cells (with hemozoin) measured by the second type of sensors.
In order to capture the resonance point of hemozoin, we conduct another measurement to tune the magnetic field in a smaller range with smaller step size and record the S-parameters of the cancellation signal (by the second type of sensors). We increase the current from 0.06 A to 0.3 A and the corresponding magnetic field increased from 30 G to 130 G, which covers the magnetic field required for resonance at around 890 MHz (approximately the center frequency of the cancellation signal of the interference system). As Fig. 5.10(a) shows, when measuring healthy red blood cells, center frequency shifts but the magnitude of cancellation signal change is within 5 dB. In other words, no obvious magnitude change in $S_{21}$ of the cancellation signal appears for healthy red blood cells. Nonetheless, when measuring the infected cells with hemozoin, a clear magnitude change of $S_{21}$ occurs at current $\sim 0.2$ A, and magnetic field $\sim 80$ G. This series of measurements is also conducted for multiple times and repeatable results are obtained.
Fig. 5.10 $S_{21}$ of the interference system, when sweeping in smaller magnetic field range (from ~ 30 G to ~ 130 G). (a) Healthy red blood cells measured by the second type of sensors. (b) Infected red blood cells (with hemozoin) measured by the second type of sensors.
5.4 Conclusions

This series of experiments has proved that our sensors and system could be used to differentiate healthy red blood cells and infected ones with hemozoin by both center frequency shift and magnitude change of $S_{21}$ of the cancellation signal. This method also shows potential to differentiate samples with different concentrations and cell populations. In the future, we need to understand more about the different behaviors of red blood cells and malaria infected cells in magnetic field. Main focus of the future work is improving sensitivity and quantifying measurement results.
CHAPTER 6

SUMMARY

In this work, novel RF sensors are presented for detecting thin films in liquid, confined liquid material, healthy and infected red blood cells. Motivations and inspirations of these sensors, especially from biochemical and biomedical science, are illustrated. Fabrication processes of each sensor are elaborated in details. Measurement setups based on on-chip interference system are built and demonstrated for characterization. Simulating and measured results are presented and discussed.

These preliminary results show the capabilities of RF sensors to detect different materials with relatively high sensitivity. RF sensors have great potential to be applied to detect minute change in dielectric properties of a small amount of MUT in a cost-efficient and fast manner. On the one hand, sensitivity of the interference system can be further improved by stabilizing the $S_{21}$ signal at a deeper cancellation level. Right now we are using external components in the system. They are helpful in controlling the balance of two branches. However, the creeping effect impedes the stability of the signal. Therefore, stable signal level is promising if the imperfections are eliminated in the future. One the other hand, spatial resolution can be improved by scaling down the sensor sizes when micro/nano fabrication is involved. If the sensing area is considerably small, single cell characterization and cell membrane micro domain imaging will be achievable.

In terms of analysis expertise, future effort will be focused on quantifying the detection results. With the ability of more sensitive sensors and accurate systems,
information related to samples’ dielectric spectroscopy will be obtained from the scattering parameters we get directly from the interference system. We suppose information such as concentration and relative permittivity of a certain liquid mixture can be extracted. The minute variation residing in cell membrane micro domains will also be differentiated.
BIBLIOGRAPHY


