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Table of contents

List of Figures

ABSTRACT OF THE THESIS

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by

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Master of Science in Nanoengineering

University of California San Diego, 2018

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This research will develop a method for continuous, accurate, and non-invasive central blood pressure waveform recording using a stretchable ultrasound device worn on the human skin. The proposed research is one of the first studies to use a wearable system to capture medical data underneath the skin. It will be the first study to implement the ultrasound functionality in stretchable electronics. We will demonstrate, by combined innovative strategies in materials science, mechanical design, and electronics integration, a stretchable transducer array based on piezoelectric materials that detect the blood vessel diameter changes and translates the information into blood pressure waveforms. We will first design and optimize the performance of a single ultrasonic transducer for measuring the central blood pressure

waveform. Then, we will develop phased array control algorithm on a stretchable platform for enabling beam focusing and improving sensitivity. In the final phase of this research, we will integrate a stretchable transducer array with the phased array control algorithm for continuous and accurate blood pressure waveform monitoring. The use of a soft, stretchable platform that matches the softness of the human skin will make a key difference in patient acceptance in high-risk populations and in wellness monitoring for the general public, with a direct impact on clinical and preventive care practices. The easy access to blood pressure waveforms will shift the public perception of the concept of blood pressure and provide unprecedented data for medical professionals, which translates into a significant reduction in associated mortality and healthcare costs.

Introduction

This research will develop a method for continuous, accurate, and non-invasive central blood pressure waveform recording using a stretchable ultrasound device worn on the human skin. Continuous central blood pressure waveform monitoring provides critical and direct diagnostic clues to cardiovascular pathological conditions, and can raise patient awareness, help preventive care, and serve as the basis for personalized medicine. This research is distinct from other blood pressure waveform measurement methods because it provides accurate waveform data with a non-invasive device that does not constrict natural body movement or cause discomfort. The proposed research is one of the first studies to use a wearable system to capture medical data underneath the skin. It will be the first study to implement the ultrasound functionality in stretchable electronics. We will demonstrate, by combined innovative strategies in materials science, mechanical design, and electronics integration, a stretchable transducer array based on piezoelectric materials that detect the blood vessel diameter changes and translates the information into blood pressure waveforms. We will first design and optimize the performance of a single ultrasonic transducer for measuring the central blood pressure waveform. Then, we will develop phased array control algorithm on a stretchable platform for enabling beam focusing and improving sensitivity. In the final phase of this research, we will integrate a stretchable transducer array with the phased array control algorithm for continuous and accurate blood pressure waveform monitoring. The use of a soft, stretchable platform that matches the softness of the human skin will make a key difference in patient acceptance in high-risk populations and in wellness monitoring for the general public, with a direct impact on clinical and preventive care practices. The easy access to blood pressure waveforms will shift the public perception of the concept of blood pressure and provide unprecedented data for medical professionals, which translates into a significant reduction in associated mortality and healthcare costs.

Chapter 1

1.1 Clinical significance of measuring blood pressure

The research objective of this proposal is to design and fabricate a wearable ultrasound Blood Pressure (BP) monitor that is able to bring non-invasive, accurate, and continuous monitoring and healthcare to population with abnormal BP. This wearable BP monitoring device is of high significance for public health, because hypertension is estimated to account for 6% of death worldwide and is often named 'silent killer' by virtue of its unnoticeable early symptoms and will greatly induce heart attack, stroke, and target organ damage[1]. Moreover, even in medically advanced countries, over 80% people[2] are not seriously realizing this gravity and have no strategy to take care of their BP, thus causing heavy breakdown on not only families but also economics in society.

It is of critical value to be able to continuously monitor the BP. Conventional BP diagnosing method is essentially a sampling process with discrete data points collected in a medical professional's office. In fact, the entire diagnosis criteria and prescribed therapy are based on medical studies that selected a representative group of the population. Though this methodology has historically been working with only occasional failures so far, like any sampling process, loss of information is unavoidable. For instance, it is argued that certain gender, race, and ethnicity groups are underrepresented[3] in data analyses and associated new drug tests. Even for the same patient, the overall health[4], metabolism rate[5], arousal, and emotion[6] are ever changing. Continuous monitoring of BP will be an enabling technology for personalized medicine and empowering tool for medical practitioners. The unprecedented amount of data collected will provide an effective means to treat and even prevent the hypertension from its outbreak.

Wearable BP monitor based on ultrasound has its unique strength over other measurement devices due to its merits in portability and continuous monitoring platform. Presently many traditional techniques can measure BP, albeit well established, still tethered by several heavy limitations while machined into wearable format. First, invasive technique by arterial catheters will give rise to pain and inflammation[7]; Second, sphygmomanometer is bulky in view of arm cuff. Besides, the information-obtaining capacity is limited. That is, instead of capturing the full BP waveform which contains many vital information, it can only measure the systolic and diastolic BP value[8]; Third, tonometer is heavily influenced by cross-talk between each pressure sensing element[9]; Forth, with respect to huge and unstable gap between photodiodes and skin, photoplethysmography (PPG) is susceptible to environmental moisture and movement artifacts during measurement[10].

Wearable ultrasound BP monitor, based on capturing the artery diameter change waveform that is converted to BP waveform, is capable of ironing out those aforementioned limitations one by one. First and foremost, ultrasound is non-invasive and non-radiation[11]. Second, ultrasound transducer can track the entire process of vessel distension so that comprehensive information corresponding to human circulatory system status can be fully captured. Third, ultrasound transducer can be machined to multichannel array style that is able to solve the cross-talk problem. Forth, loaded onto a soft and conformal format, this device has a unique strength over other wearable device that is able to achieve intimate contact with epidermis, thus minimizing the motion artifact and the influence of environment. In all, this novel device, with premium convenience, comprehensiveness, and preciseness, which is able to monitor the intention of that ‘silent killer’ and then detect it before its outbreak, can not only save billions of lives but also reduce the expenditure of worldwide medical system.

1.2 Innovation of the project

Health and wellness monitoring devices that mount on the human skin are of great historical and continuing interest in clinical health care, due to their versatile capabilities in noninvasive and physiological diagnostic applications. We are focusing on materials and fabrication for wearable and mechanically invisible devices that exploit conventionally rigid and brittle building blocks. The key design features involve thin soft silicone elastomer as the substrate, multilayered serpentine structures as the interconnects, and a novel liquid/soft-polymer packaging scheme to isolate the strain at the hard component/soft substrate interface [12]. Such devices are locally rigid but globally compliant, and can laminate and adhere on the skin via van der Waals forces alone. The result is a natural interface that is capable of accommodating the motions of the skin with minimal mechanical constraints, thereby establishing not only a robust, non-irritating skin/electrode contact but also the basis for intimate integration of diverse classes of electronic and sensor technologies directly with the human body.

A variety of wearable sensors for health relevant parameters have been demonstrated in the literature, such as temperature [13], pH [14], hydration [15], glucose/lactate [16], local field potentials [17], which are all focused on physiological signals from the surface of human body, without any insights into the deep tissues/organs of the joints. Recently, there have been many reports on flexible ultrasound devices based on micromachined ultrasound transducers [18], such as capacitive micromachined ultrasonic transducers that can vibrate by a field-induced electrostatic attraction between suspended membrane and the substrate [19], and piezoelectric micromachined ultrasonic transducers that can vibrate by piezoelectrically induced membrane actuation in d31 [20] or d33 mode [21]. However, all of these transducers were limited by their large size and modest uniformity and performance.

In this project, an "island-bridge" design is explored to incorporate the high performance rigid piezoelectric materials. Specifically, the rigid components are integrated with the islands, and the wavy serpentine bridges absorb the externally applied strain. So the entire structure is rigid locally (with a foot print of 1.8 mm by 1.8 mm), but flexible/stretchable globally by adjusting the spacing between the rigid islands during the bending, stretching, and twisting processes. This enabling technology bridges the gap between traditional rigid planar high performance electronics and the soft curvilinear dynamic biological objects.

Chapter 2 Single transducer blood pressure measurement

It has been known that blood pressure has a positive relationship with arterial diameter, which can do the substitution of blood pressure[22]. Based on this principle, we design a device as Fig. 1, which can capture the artery diameter changing by transmitting and receiving ultrasound signal and transform this shifting to blood pressure. From the top to the bottom, the soft ultrasonic probe consists of superstrate, interconnect, conductive backing material, piezoelectric transducer element, interconnect, acoustic matching layer, and substrate (Fig. 1(a)).

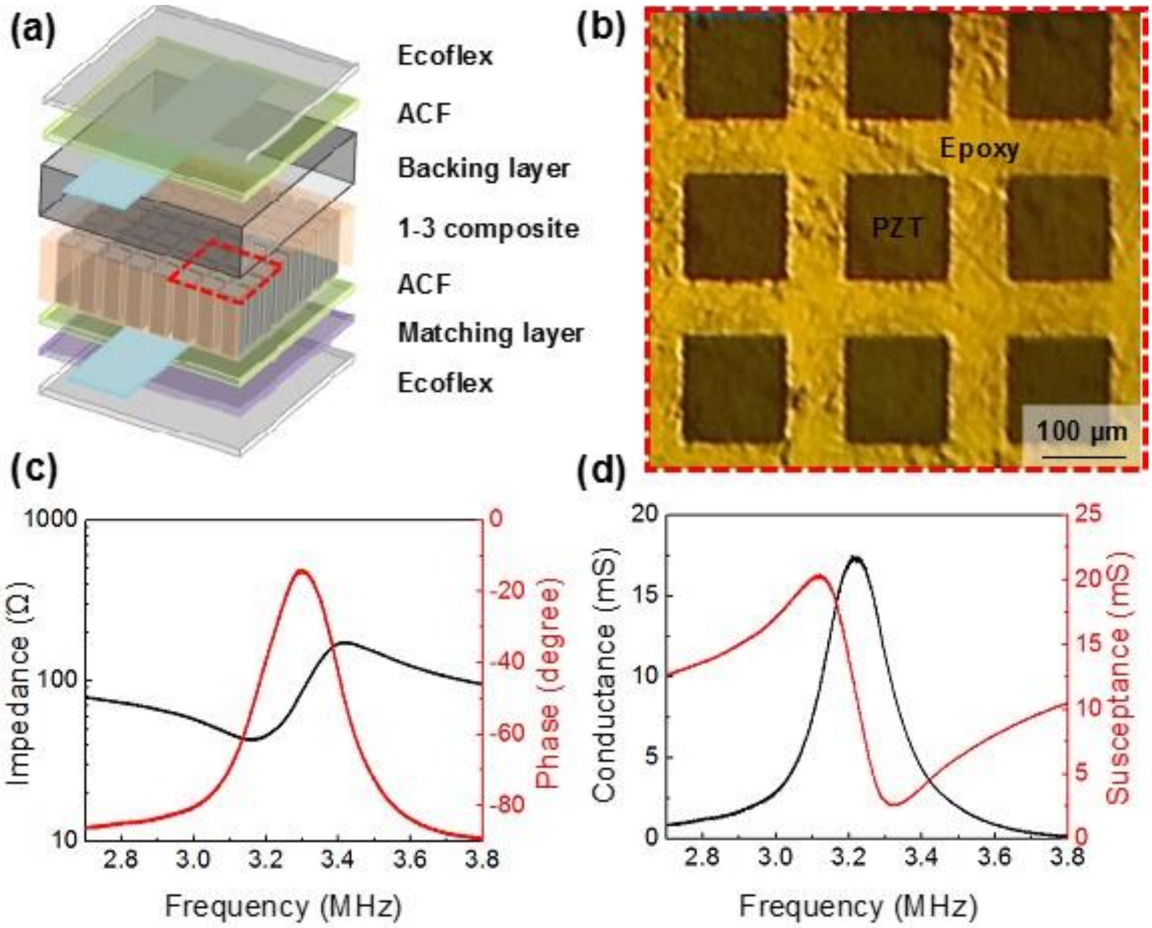

Figure 1.1: Structural layout and characterization of soft ultrasonic transducer (a) Exploded view of one pixel in the ultrasound probe. (b) Optical image of the 1-3 composite. Frequency dependence of (c) impedance and phase and (d) conductance and susceptance of the 1-3 composite.

The substrate and superstrate are both Ecoflex for its high stretchability and high resilience to defects [23]. The Young's modulus and the acoustic impedance of the Ecoflex are also close to these of the human body [24]. The interconnects based on anisotropic conductive films (ACF) [25] provide electrical connection between the transducer elements. The backing material will dampen the ringing effect from the backside of the piezoelectric transducers, reducing excessive vibration [26]. This will allow the elements to generate ultrasonic waves with shorter pulse length, improving axial resolution of the images. A very lossy conductive epoxy (E-SOLDER 3022 [27]) is cast and cured on the elements, as the backing material. The 1-3 lead zirconate titanate (PZT)-epoxy composite [28] is chosen as the transducer element because of its superior performance to piezoelectric polymers, and also its capability of avoiding lateral modes and grating lobes. The size of each PZT element is 100 µm x 100 µm with a pitch of 60 µm Fig. 1(b). The frequency dependences of impedance, phase, conductance, and susceptance of the composite, characterized by impedance analyzer, are shown in Fig. 1(c) and 1(d). The working frequency is around 3.3 MHz, and the impedance at the working frequency is close to 50 Ω that matches the impedance of the source instrument [29]. The matching layer, with intermediate acoustic impedance between the rigid piezoelectrics and the soft biological tissue, helps enhance the transportation of acoustic wave through the device/skin interface. For a given frequency, the matching layer thickness should be one quarter of the acoustic wavelength and its impedance should be the geometric mean of these of the piezoelectrics and the targeted tissue. TiO2 nanoparticle/polyimide composites are commonly used as the matching layer, whose impedance can be continuously tuned, generally in the range of 2-15 MRayls, by adjusting the composition.

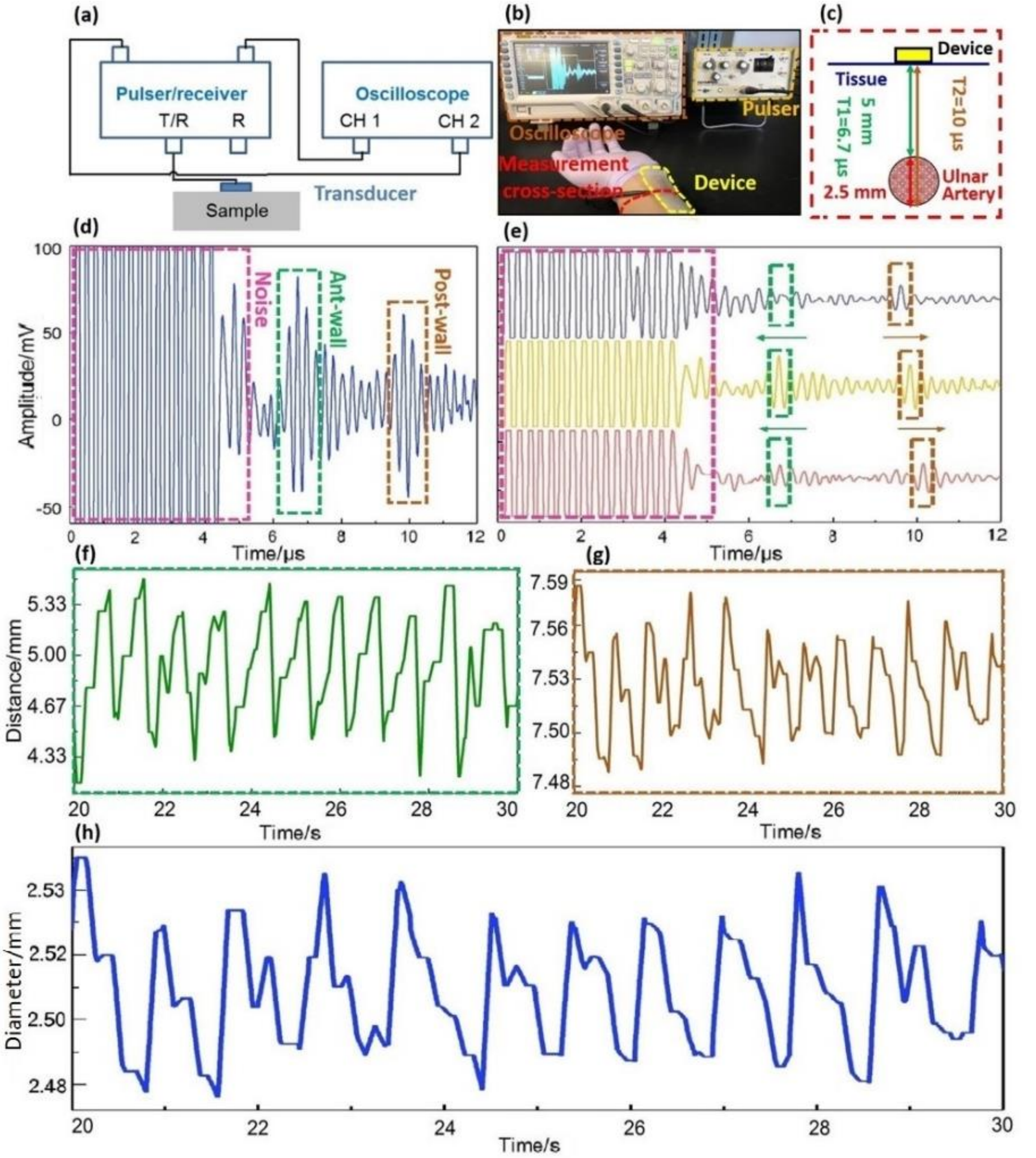

Figure 2.1: (a) Schematics of experiment. (b) Experiment phantom (c) Reflected signal from human wrist (d) Vessel wall shifting represented by peak position motion (e) Schematics of measurement cross-section (f) The waveform of anterior wall (represented by the propagation distance between ant-wall and transducer) (g) The waveform of posterior wall (represented by the propagation distance between post-wall and transducer) (h) Vessel diameter waveform

As a preliminary test, a flexible ultrasound device was fabricated which is able to not only register pulse but also receive back-propagate signal. By laying the device overlay any tissue, it can receive echo from many internal interfaces. To prove this process, we directly put it onto human wrist to test its feasibility and accuracy using ultrasound Time of Flight (TOF) to locate interfaces in the tissue, especially for locating the location of vessel wall. In the experiment as Fig 2 illustrated, we put our device on human wrist to detect the peak shift of real vessel wall. Human's ulnar artery has an approximate diameter of 2.0 mm and with a diameter distension ratio of 10% [30] which means the diameter distension is about 0.2 millimeter. Fig 2 (a) is the schematics of the experimental apparatus. Fig 2 (b) is the experimental setup Fig 2 (c) is back-propagated signal with two identifiable peaks corresponding to the arterial and posterior wall of real ulnar artery. Fig 2 (d) is three back-propagated signal with different peak position meaning different diameter of the vessel in a cardiac cycle. Fig 2 (e) is the schematics of the measuring cross section. The distance between anterior wall and epidermis is 5 mm, and the ultrasound has the velocity of 1540 m/s in tissue. Fig 2 (f), (g) are the achieved waveforms by extracting the anterior and posterior walls' peak position (in time domain) and then transform it to distance by ultrasound velocity. Fig 2 (h) is the full vessel diameter waveform achieved by subtract the upper two distance waveform. With good correspondence with actual geometry of tissue, those results indicates that during human cardiac cycle, the accurate measurement on diameter shifting of ulnar artery can be achieved. Then after transforming algorithm is added, the vessel diameter waveform can be translate to BP waveform ultimately.

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