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Development and Fabrication of a 3-French Photoacoustic Catheter for Imaging Mouse Colon

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Abstract*—Colon cancer is the third most common cancer in the world, if skin cancer is not considered. Despite the high incidence and high mortality rate, most of the outcomes could be prevented by using accurate techniques for early cancer detection to enable early treatment. In this context, it is important to conduct preclinical studies, using animal models of colon diseases, to test new diagnostic approaches including imaging instrumentation. We have previously used a 3-French ultrasound IVUS catheter to image the layered structure in the mouse colon, detect polyps, and visualize their invasion through the colon wall. Now we aim to add photoacoustic (PA) imaging with a miniaturized probe designed for combined micro-ultrasound (micro-US) and (PA) imaging of the mouse colon. For this purpose, a mini US probe was manufactured to fit a previous system used before.

Keywords— Colon cancer, mouse, micro US, Photoacustic.

I. Introduction

Colorectal cancer is among the third and fourth most common type of cancer diagnosed worldwide [1]. The American Cancer Society Institute estimated 1,762,450 new cases of cancer in the US in 2019 and 606,880 deaths as a result of the disease [1], with colorectal cancer being the third most frequent cancer in men and the second among women. Despite the high incidence and high mortality rate, more cases of colon cancer could be prevented by improving diagnostic techniques for early detection and follow-up [2-5].

The standard procedure for the diagnosis of lesions and tumors in the intestinal mucosa is colonoscopy. However, endoscopic examinations are not always able to identify small lesions, especially non-polypoids and other lesions located inside the colon wall [3-6].

It is important to conduct preclinical studies, using animal models of colon diseases, to test new diagnostic approaches including imaging instrumentation. Therefore, imaging devices to be used in studies of mouse models of colon disease must account for the small dimensions of the mouse colon lumen and must be able to accurately resolve and display the layers of colon wall.

An ultrasound (US) imaging system employing a 3-French mini-probe catheter, normally used for intravascular ultrasound imaging (IVUS) and operating at 40 MHz frequency, has been previously used to image the layered structure in the mouse colon, detect polyps, and visualize their invasion through the colon wall [4]. In addition, a 3-French dual frequency mini transducer designed for use in small animals was recently manufactured [7]. The target now is to add photoacoustic (PA) imaging to visualize the blood pool and PA contrast agents. Photoacoustic imaging combined with micro-ultrasound has the potential to detect blood and blood oxygenation, and to image deeper tissue structures than conventional optical endoscopic techniques.

The design and development of a miniature photoacoustic endoscopic probe are explored in this present work. The configuration of a photoacoustic probe suitable for incorporating an optical fiber cable for illuminating tissue is discussed. Then the steps related to the manufacturing of the US piezoelectric element and the interconnection between the transducer and the electrical cabling are presented. The specifications of size and operating frequency of the US piezoelectric element are based on previous experiences [4-7]. The manufactured miniature transducer was characterized with measured electrical impedance and pulse-echo signal.

II. Probe Design and Fabrication

A. Endoscopic probe design

The challenge consists in fitting a miniature photoacoustic endoscopic probe into a catheter that must be introduced within the 1.0 mm diameter working channel (3 French in diameter) of a miniature endoscope for *in vivo* colonoscopic, PA imaging and US imaging of the mouse colon. The design of the miniature photoacoustic endoscopic probe follows previous reports, as in [8-9], with the requirement of a smaller outer diameter. For PA imaging, an optical fiber is incorporated into the probe to transmit laser pulses at a single wavelength in the range of 800 nm for illumination of the tissue to generate the PA signal. This wavelength is the isosbestic point for blood, and allows imaging of total hemoglobin content. For this device design, a single laser wavelength is used so that the laser pulse repetition rate could be as high as possible. With fast pulse repetition rates (up to 1000 pulse/s), the ultrasound transducer can be turned within the catheter at rotation rates nearing the standard rates for IVUS imaging (state rotation rate used in your system).

The proposed design is for a thin-walled catheter, with an outer diameter of 1.2 mm. Within the catheter is a torque cable, a single 200 µm diameter optical fiber (OF), the ultrasound transducer for detecting the PA signal, and the microcoaxial cable (150 µm) that is connected to the US piezoelectric element. The design and configuration of the components are shown in the Fig. 1(A-B). All these components were designed and must fit within the 1.2 mm outer diameter catheter, which restricts the US transducer element to 0.5 mm wide by 0.5 mm thick and 1.2 mm of length, as indicated in Fig. 2(A-C). The design of the electrical interconnect between cable and transducer is adapted from a previously developed dual frequency IVUS probe [7]. The microcoaxial cable is positioned within a channel created in the conductive backing of the transducer. Another, perpendicular, channel serves to isolate the signal connection from the ground connection.

B. US Transducer fabrication

A bulk plate of lead-zirconate-titanate (PZT-5H), with initial thickness of 1 mm, was lapped down using Al_2O_3 slurry on a LP50 Precision Lapping System (Logitech, Glasgow, UK), keeping the electrode on one side. The target thickness was 50 µm and the achieved final thickness was 54 µm. Then, 300 Å of chrome and 300 Å of gold was sputtered onto the front surfaces (AJA International, Scituate, MA, USA), to create an electrode and signal connection in the front face of the transducer. The matching layer, made with conductive epoxy (Epotek H20e, Epoxy Technology Inc., Billerica, MA), was deposited over the electrode and lapped down until thickness of 14 µm, as measured with a micrometer. Then, the sample was flipped over and covered with the conductive epoxy backing layer (Epotek H20e), at least 400 µm, cured for 8 hours in the oven at 80°C. After making the transducer, 3 mm x 1 mm strips were produced using a precision dicing saw (DAD 3240, DISCO Hi-Tec, Tokyo, Japan), with a 300 µm blade, to define the individual transducers from the larger plate.

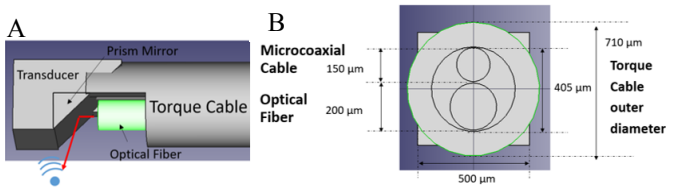

Fig 1. A. Design of US/PA imaging device with the US transducer electrically connected to Microcoaxial Cable, the Optical Fiber and the Torque Cable. **B.** The dimensions are suitable for the probe to fit in the 1.2 mm diameter working channel of a mini endoscope.

C. Microcoaxial Cable Connections

The approach used for connecting the microcoaxial cable to one transducer element demarked by the strip sides is based on the schematic drawing shown in Fig. 2(A-C). The precision dicing saw, with a 300 µm blade, was used to create two perpendicular channels through the thickness transducer backing layer on the back side of the transducer. The first is the insulating channel, cut along the width of the element though the H20E backing, the back face electrode and into the PZT. The second is the signal channel, which is only cut though the backing layer from the back face and just to the electrode on the PZT surface. The insulating channel is shorter and isolates ground and signal zones on the transducer by separating the back electrode on PZT surface. The signal channel continues the length of the transducer element, and is used for connecting the microcoaxial cable inner conductor and ground shield to the PZT back face. The microcoaxial cable was introduced into the signal channel, with the exposed length of the inner conductor contacting only the end of the signal channel belonging to the signal zone. Then, the same conductive epoxy employed previously, was used to connect the tip of the microcoaxial cable inner conductor with the conductive epoxy backing layer.

The next step followed with the connection of microcoaxial cable shielding mesh conductor to the transducer front face electrode (ground), also using conductive epoxy. With the electrical connections made to the microcoaxial cable, then the channels were filled with non-conductive epoxy (353 ND epoxy, Epoxy Technologies) and cured. After this process, the single element transducer containing the full set of matching layer, PZT element and backing layer was diced to final thickness of 400 um. To release the transducer from the lapping carrier, the transducer was cut though its full thickness and cut down to its final size. Details for the layers of the transducer are shown in Fig. 2(A), corresponding to the designed dimensions, and as a picture in Fig. 2(D). The miniprobe is shown in the same orientation, and with these images it is possible identify the non-conductive channel, the front face, the back face and the Microcoaxial cable on the fabricated device.

III. Transducer Characterisation

A. Electrical impedance

The electrical impedance of the mini transducer was measured using the Vector Network Analyzer (E5061B, Agilent Technologies, Santa Clara, CA, USA). The effects of the instrument probing cable were corrected by applying fixture compensation measurements.

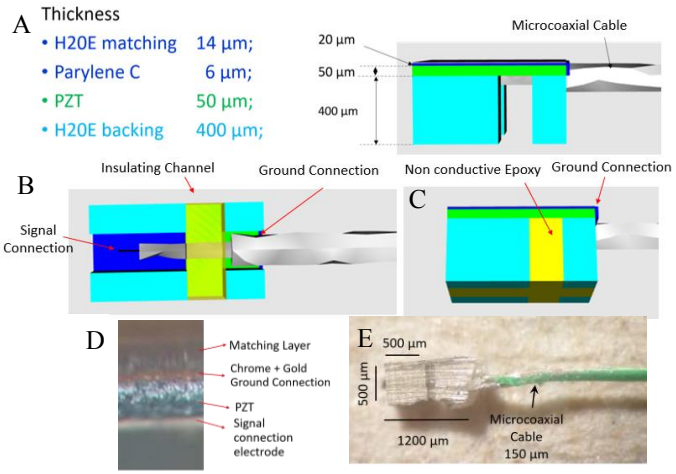

Fig 2. A. Diagram of transducer after element fabrication and prior to electrical connection to coaxial cable showing layers and designed layer thicknesses. **B**. Diagram of the transducer, backing layer with the channel for the Microcoaxial inner conductor is connected and showing the insulating channel, cut through the PZT backing layer and electrode. **C**. Illustration of the non conductive epoxy filling the insulating channel and covering the signal and ground electrical connections in the longer channel. **D.** Microscope image (20x) of the transducer layers: matching layer (H20e), sputtered chrome and gold layer, to make ground connection with PZT, PZT and the signal connection electrode. **E**. Photo of the manufactured mini-transducer connected to microaxial Cable.

The plots for the measured electrical impedance magnitude and phase of the transducer are depicted in Figure 3. It is noticed that the resonant frequency is at 36.0 MHz.

B. Pulse-echo characterization

The pulse-echo test was performed with the mini transducer fixed in a holder looking upward and a deionized water drop placed on the transducer face. The echoes from the interface between the water drop and air were acquired. The excitation signal was generated by an arbitrary waveform generator (AWG2020, Tektronix, Beaverton, OR, USA), with its output signal amplified by a power amplifier (Model 3205, AMT, Anaheim, CA, USA). The transmitting and receiving circuit networks were separated using an expander and limiter. The transducer was connected between the expander and limiter and in parallel with a 50 Ω load. The echo signals received by the transducer passed through attenuators (Minicircuits, Brooklyn, NY, USA), a preamplifier (AU1579, Miteq, Hauppage, NY, USA), a 1 MHz 4th-order high pass filter and 100 MHz low pass filter (Minicircuits) before being digitized (DP210, Acqiris, Plan-les-Ouates, Switzerland).

Figure 4 contains the plot of the echo signal (A) and the corresponding frequency power spectrum, normalized by its peak, (B). It is noticed the power spectrum centered at 48.7 MHz and the -6 dB frequency bandwidth corresponds to 7 MHz.

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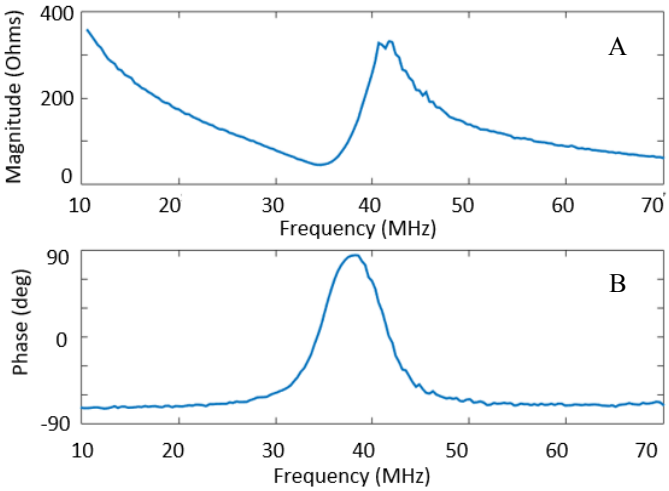

Fig. 3. Measured electrical impedance magnitude (A) and pahse (B).

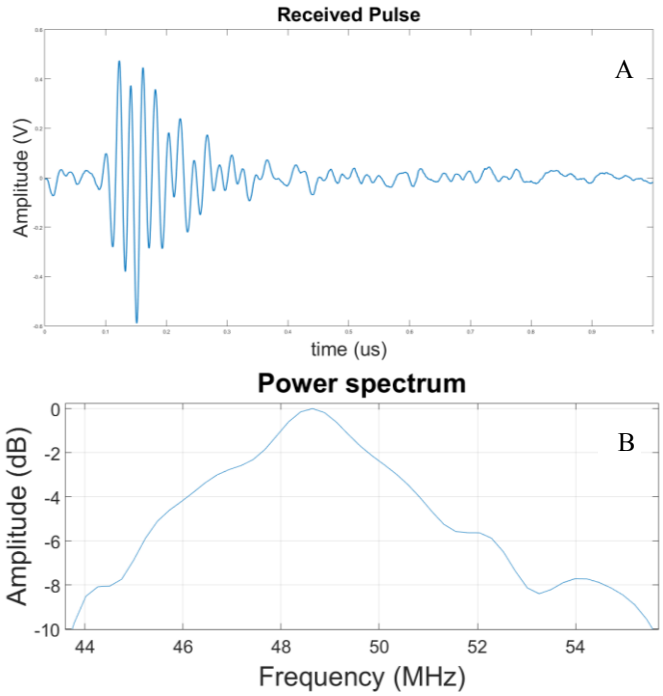

Fig. 4. Echo signal of the mini transducer (A) and corresponding frequency power spectrum normalized to its peak (B).

IV. Discussion

Previous ultrasound imaging of mouse colon, with systems operating at 40 MHz, showed enough resolution to be used to detect cancerous polyps. The collection of cross-section images acquired following a pull-back approach to generate volumetric images has allowed visualization of the anatomic shape and lesions in the colon, as well characteristics of the layers. These systems require miniature transducers, as part of preclinical studies of colorectal cancer or other diseases of the bowel. Thus, the combined PA and micro-US system can be suitable for imaging tumors in mice colon and acquiring images of tumor vascularization.

The designed device has dimensions suitable for placing the probe within the 1.2 mm working channel of the miniature

endoscope used for pre-clinical colonoscopy. The working frequency of the mini-probe manufactured is in accordance with the previous work, close to frequency designed, and with a – 6dB frequency bandwidth of 7 MHz. The noise in the signal of the received pulse, shown in Figure 4A, can be attributed to not having a planar reflective surface. The impedance of the transducer, when connected to the coaxial cable, was approximately 50 ohms at 36.0 MHz.

V. CONCLUSION

The PA mini-probe was designed to work at 40 MHz, in accordance with previous work that demonstrate adequate detection of layers in the colon of small animals from the ultrasound images. The present work presents the PA mini-probe concept and details the steps to manufacture the US transducer component of the PA mini-probe. The manufactured US transducer performed in compliance of the requirements in size, to fit the mini-probe catheter used during image acquisitions of the colon of small animals, and with an operating frequency suitable for differentiating the tissue layers and polyps in the mouse colon.

The next steps for this work comply in adding the optical fiber and the torque cable to the mini-probe and in incorporating the catheter.

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