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All-optical multimode fibre photoacoustic endomicroscopy with scalable spatial resolution and field-of-view

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1. Introduction

Medical endoscopy is commonly used for examining internal tissue and diagnostic procedures such as biopsies. However, clinical white-light endoscopes only provide visualisation of the tissue surface. Definitive histopathological analysis is currently required and relies on extracting tissue samples during a biopsy procedure. Advanced optical endoscopy modalities such as endoscopic optical coherence tomography and confocal fluorescence endomicroscopy have been investigated to provide tissue characterisation *in situ*. However, although proven useful for certain applications, these modalities suffer from either a lack of molecular contrast or a challenge with depth-resolved information. In the past two decades, photoacoustic imaging (PAI) has emerged as a promising tool in various pre-clinical and clinical applications. Different from purely optical imaging modalities, PAI is based on the optical absorption contrast and has highly scalable spatial resolution and tissue penetration depth owing to its ultrasound-based collection. These properties make it applicable in a wide range of clinical disciplines including cardiology, oncology, and neurology [1-3]. However, although conventional non-invasive photoacoustic tomography systems with extracorporeal illumination possess large tissue penetration depths up to several centimetres, the tissue penetration depths of optical-resolution photoacoustic microscopy systems that rely on a focused laser beam are limited to ~1 mm beneath the tissue surface, which may hinder clinical translation. To extend the clinical applicability of PAI, photoacoustic endoscopes (PAEs) were developed for examining internal tissues with high spatial resolution and minimal invasiveness [4,5]. While side-viewing PAEs intended for imaging arteries and gastrointestinal tracts attracted the most attention, forward-viewing PAEs are more suitable for the guidance of surgical procedures such as needle biopsy. Early forward-viewing PAEs employed multi-core coherent fibre bundles with imaging being accomplished by raster-scanning a focused laser beam between the distal ends of the individual cores [4]. Recently, multimode fibres (MMFs) were reported in forward-viewing PAE and a focused laser beam was delivered through a MMF using wavefront shaping [6], leading to an improved spatial resolution, and reduced costs and probe sizes compared to multi-core fibre bundles. In this work, we developed a high-speed, all-optical photoacoustic endomicroscopy (PAEM) probe using a digital micromirror device for wavefront shaping. Excitation laser light was focused and raster-scanned through a multimode fibre via wavefront shaping, whilst the optically excited ultrasound was received with a fibre-optic sensor. The two fibres were integrated within the cannula of a 20-gauge medical needle. High-resolution imaging on mouse red blood cells (RBCs) and mouse ear vasculature ex vivo was achieved. We also demonstrated the high scalability in terms of spatial resolution and field-of-view (FoV) by varying the distance of the focal plane to the distal end of the MMF using wavefront shaping.

2. Methods

1.1. Wavefront shaping algorithm

Since mode dispersion scrambles coherent light transport through MMFs, the MMF was calibrated for shaping the transmitted light into a tightly focused beam prior to imaging implementation. The calibration method was detailed in our previous works [7]. Here briefly, a series of binary masks constructed using Hadamard patterns were applied to the micromirrors of a digital micromirror device (DMD) to modulate the wavefront of the excitation laser and projected onto the proximal fibre tip while the corresponding output speckles were recorded by a camera. Based on these input-output pairs, the light intensity changes through the MMF were modelled as a real-valued intensity transmission matrix (RVITM). Then, optimal DMD patterns that could modulate the incident optical wavefront to focus light at desired spatial locations through the MMF were determined.

1.2. Experimental setup

The configuration of the PAEM system is shown in Fig. 1. The PAEM probe comprises a MMF for the delivery of

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excitation laser and a fibre-optic ultrasound sensor relying on a planoconcave microresonator at the tip of a single-mode fibre [8]. Both fibres were integrated within the cannula of a 20-gauge needle. The wavelength of the excitation laser light was 532 nm with a pulse duration of 2 ns (SPOT-10-200-532, Elforlight, UK). After beam expansion with two lenses (f = 30 mm, AC254-030-A-ML; f = 50 mm, AC254-030-A-ML, Thorlabs, New Jersey) and an iris, the laser light was reflected and spatially modulated by a DMD (768×1080, DLP7000, Texas Instruments, Texas). A 30 cm-long MMF (φ100 μm, 0.29 NA, Newport, California) was used to deliver the excitation laser light, with the modulated light projected onto the proximal fibre tip through a convex lens (f = 50 mm, AC254-050-A-ML, Thorlabs, New Jersey) and an objective (20×, 0.4 NA, RMS20×, Thorlabs, New Jersey). A fibre characterizing module comprising a camera (C11440-22CU01, Hamamatsu, Shizuoka Pref. Japan), a convex lens (f = 100 mm, AC254-100-A-ML, Thorlabs, New Jersey) and an objective (20×, 0.4 NA, RMS20×, Thorlabs, New Jersey) was used to record the transmitted light through the fibre. A sub-region of the DMD covering 128×128 micromirrors was employed to modulate the laser light. The wavefront shaping algorithm was implemented to characterize light focusing at multiple planes with varying distances to the fibre tip. After MMF characterisation, the characterisation module was removed, and a 1951 USAF Resolution Test Targets (Thorlabs, New Jersey, USA) was placed at the optical focusing plane. The excited ultrasound was received by delivering a wavelength-tunable continuous wave laser (TSL-550, Santec, UK) to the microresonator and the reflected light through an optical circulator (6015-3-APC, 1525-1610 nm, Thorlabs, New Jersey) was received by a photodiode (G9801-22, Hamamatsu, Shizuoka Pref. Japan). The reflected light representing ultrasound signals, was digitized by a data acquisition card (M4i.4420, Spectrum Instrumentation, Grosshansdorf, Germany) and then transferred to a personal computer (Intel i7, 3.2 GHz) for processing. The synchronization control of the imaging system was achieved by a waveform generator (33600A, Keysight, Santa Rosa, California) and a custom MATLAB program.

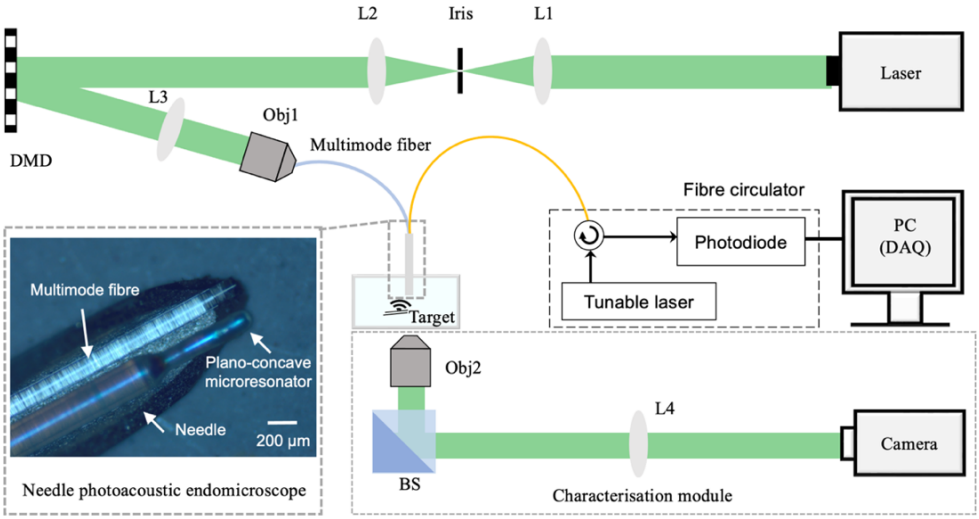

Fig. 1. Configuration of the photoacoustic endomicroscopy system. L1-L4, lenes; DMD, digital micromirror device; Obj 1-2, objectives; BS, beamsplitter; DAQ, data acquisition.

3. Results & Discussion

MMF characterisation was performed using a high-speed algorithm developed by the author's group, namely real-valued intensity transmission matrix [7]. It took ~ 3 min to characterise the MMF for raster-scanning at 7850 spatial positions. The DMD was operated at 10 kHz leading to an imaging speed of ~1 frame per second (including signal processing). Examples of PAEM images are shown in Fig. 2. The biconcave structures of RBCs were clearly visualised with image fidelity comparable to benchtop photoacoustic microscopy [9]. The structures of micro-vasculatures with vessel diameters around 10 μm in a mouse ear were also apparent. In this case, signals were averaged with 64 sequential measurements for higher signal-to-noise ratio. The use of a MMF for delivering the excitation laser greatly improved the lateral resolution and reduced the probe size and cost compared to those based on coherent fibre bundles. And owing to the use of a high-speed DMD for wavefront shaping, the imaging speed was improved by more than two orders of magnitude as compared to that achieved with a commonly used liquid-crystal spatial light modulator. Another key component is the fibre-optic ultrasound sensor, which has much higher sensitivity than piezoelectric transducers with the same size and is capable of nearly omni-directional ultrasound detection. The small sizes of both the MMF and fibre-optic sensor allow their integration within the cannula of a 20-gauage medical needle, which could facilitate its clinical translation for guiding minimally invasive procedures such as needle biopsy.

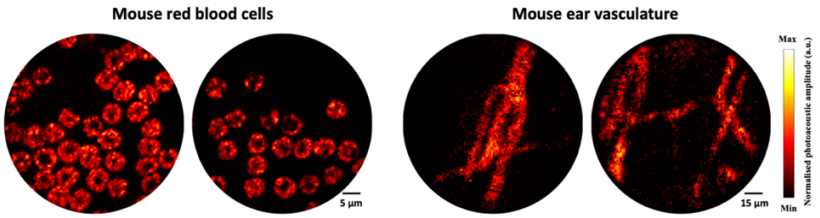

Fig. 2. Photoacoustic endomicroscopy images of mouse red blood cells and mouse ear vasculature.

The scalability of the developed imaging probe in terms of the spatial resolution and field-of-view is shown in Fig. 3. Since the laser beam was transmitted with an angle from the distal MMF tip, the FoV increased from 100 μm to 1 mm in diameter when the focal plane varied from 0 to 2.2 mm away from the fibre tip. Accordingly, the lateral resolution of the imaging probe, based on raster-scanning of a focused ultrasound excitation beam, worsened from 1.2 μm to 12 μm due to the decrease of the effective numeral aperture when the focal plane was moved away from the distal fibre tip. The scalability of the PAEM probe allows its applications in wider clinical scenarios that requires various lateral resolution and FoVs.

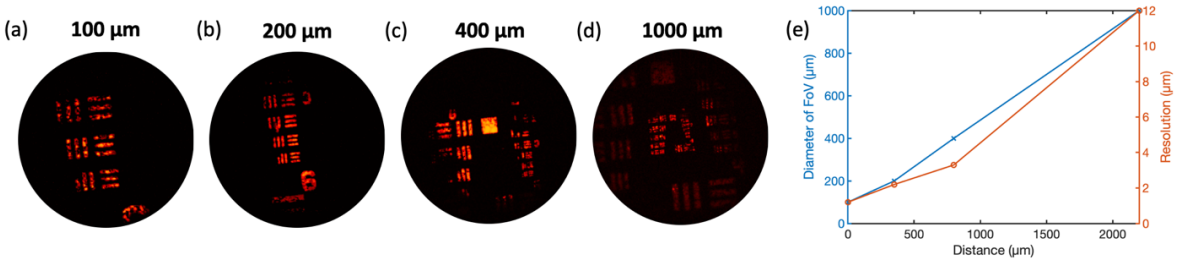

Fig. 3. The scalability of the probe. (a-d) Photoacoustic microscopy imaging results of a resolution target with varying field of view. (e) The evolution of field of view and resolution with the distance to the fibre tip.

4. Conclusion

In summary, we developed an all-optical, forward-viewing PAEM probe based on a MMF and a highly sensitive fibre-optic microresonator ultrasound sensor. High-fidelity 3D images of mouse red blood cells and ear vasculature were acquired. We also demonstrated the high scalability of the MMF-based PAEM probe for achieving a FoV that was 100 times as large as the fibre core by shaping the optical wavefronts to focus laser light with ~2 mm distance to the fibre tip with the lateral resolution retained at around 12 μm. This needle probe thus holds the potential for guiding tumour needle biopsy by examining tissue at sub-cellular spatial resolution *in situ*.

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