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Photoacoustic Imaging by Use of Micro-Electro-Mechanical System Scanner

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Abstract: Photoacoustic imaging acquires the absorption contrast of biological tissue with ultrasound resolution. It has been broadly investigated in biomedicine for animal and clinical studies. Recently, a micro-electro-mechanical system (MEMS) scanner has been utilized in photoacoustic imaging systems to enhance their performance and extend the realm of applications. The review provides a recap of recent developments in photoacoustic imaging using MEMS scanner, from instrumentation to applications. The topics include the design of MEMS scanner, its use in photoacoustic microscopy, miniature imaging probes, development of dual-modality systems, as well as cutting-edge bio-imaging studies.
Key words: photoacoustic imaging, micro-electro-mechanical system (MEMS), photoacoustic microscopy, high-speed imaging, photoacoustic endoscopy
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0 Introduction

Optical imaging of tissue provides useful information through light-tissue interactions. In the optical spectral range, tissue is a highly scattering medium. Thus, the fine resolution is restricted at low imaging depth in tissue. Alternatively, high imaging depth can be achieved by diffused light but with poor spatial resolution. It remains challenging to attain fine spatial resolution at depths by pure optical imaging. Fortunately, listening to tissue through converting light into sound waves, which are much less scattered, makes fine spatial resolution at depths possible. Absorption of light by tissue produces acoustic waves through photoacoustic effect. By detecting the acoustic waves, photoacoustic images can be acquired to restore tissue absorption information. The hybrid imaging modality is particularly useful for biomedicine because of rich optical contrasts of tissue according to its chemical composition[1-2]. Photoacoustic imaging has drawn increasing attention in the past fifteen years, and a variety of applications such as vascular biology[3-4], neurology[5], ophthalmology[6-7] and cardiology[8-9] have been explored. Compared with conventional ultrasound imaging that reveals only mechanical contrasts, photoacoustic imaging measures optical absorption contrasts which are closely related to human physiological and pathological information. Therefore, photoacoustic imaging is of significant biomedical and clinical value.

Major components of a photoacoustic imaging system include a pulsed laser, an ultrasonic transducer, data acquisition components such as a digitizer, and a computer for system control, data storage and image construction. Two major image formation methods have been used in photoacoustic imaging. The first method is inverse reconstruction based on acoustic detection at many locations, which is termed as photoacoustic computed tomography (PACT). PACT systems can be constructed using an ultrasonic array or a synthetic array by scanning. The second method is by scanning a focused transducer or a focused laser to obtain information of each scanning point, which is termed as photoacoustic microscopy (PAM) and can provide higher resolution than PACT. PAM can be further categorized into acoustic-resolution PAM (AR-PAM)[10], where a focused transducer is scanned to have lateral resolution decided by the acoustic focus, and optical-resolution PAM (OR-PAM)[11], where a focused laser is scanned to provide high lateral resolution determined by the optical focal spot size. OR-PAM provides higher lateral resolution than AR-PAM, while

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AR-PAM has deeper penetration in tissue than OR-PAM. In terms of imaging speed, a single pulse can generate a two-dimensional (2D) or three-dimensional (3D) image in PACT if the ultrasonic array is used[12]. The frame rate is determined by the pulse repetition rate and typically can achieve tens of frames per second. On the other hand, fast scanning is needed in PAM to achieve a similar frame rate as in PACT. For example, in order to acquire 100 point × 100 point within 0.1 s, the scanning rate must be at least 100 kHz. Thus, a laser with a high repetition rate as well as fast scanning is essential to realize high-speed PAM imaging.

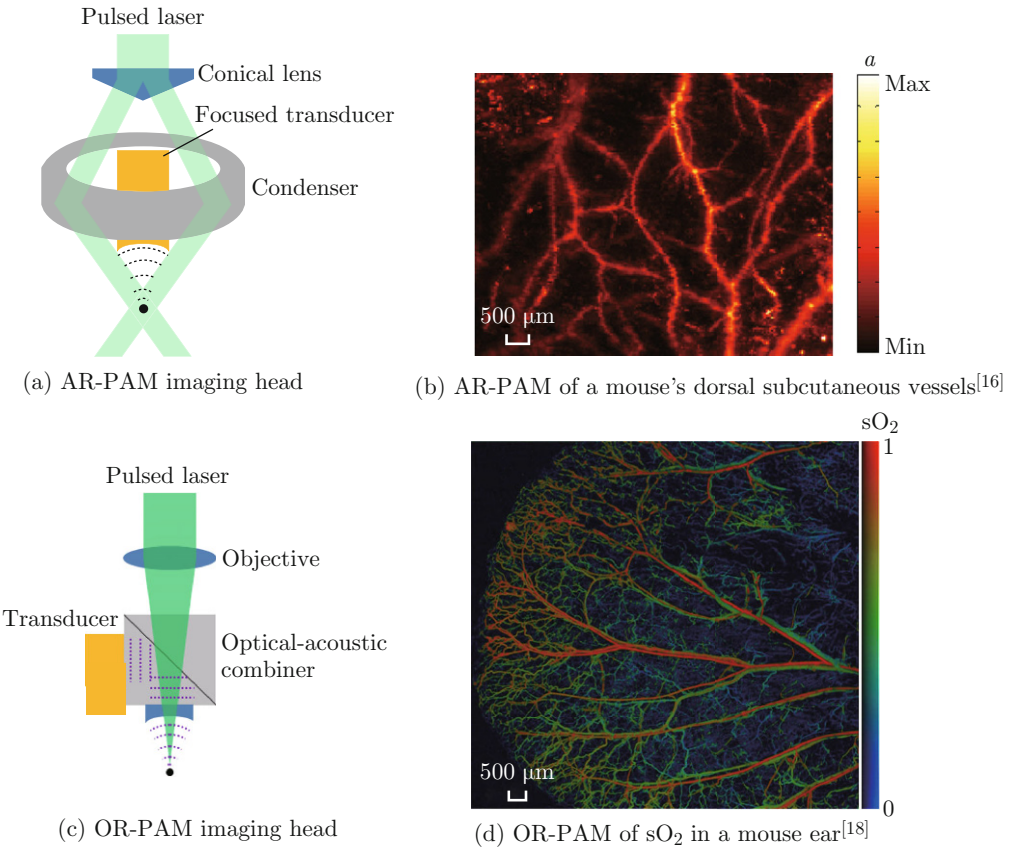
Currently, the need to perform PAM with a more user-friendly device and interface is growing as more extensive exploration of potential biomedical applications. For example, PAM conducted in an endoscopic manner or in hand-held operation has been developed[13-14]. Besides, the imaging speed mentioned above plays a key role in in vivo and clinical applications. One of the main challenges to realize the above functions and performance is the design and integration of the scanning component. A motorized stage can be used for mechanical scanning of a PAM imaging head, but such setup suffers from low speed and bulky size. A galvanometer mirror has been used to improve the speed, yet there is still a large gap to be bridged for real-time imaging[15]. With the advance of micro-electro-mechanical system (MEMS) technology, the MEMS-based scanner has brought hope to new generation PAM to realize good functionalities. The compact MEMS scanner can be integrated in a PAM system to enable fast scanning, hand-held operation or endoscopic applicability.

In this review, brief introductions are given to scanning-based photoacoustic imaging implementations and the technology for MEMS scanner. Then, the review presents the recent development of the MEMS scanner adopted in AR-PAM and OR-PAM systems. After that, we discuss the further advance of the MEMS scanner-based photoacoustics in several aspects including hand-held probes, dual-modality imaging, and novel biomedical applications. Throughout this review, recent relevant works are incorporated. Finally, a summary and a future outlook are given.

1 Scanning Photoacoustic Microscopy and the MEMS Scanner

1.1 Scanning Photoacoustic Microscopy

Mechanical scanning of the imaging head using a motorized stage can be employed to acquire 2D or 3D PAM images. For AR-PAM, as shown in Fig. 1(a), the



(a) AR-PAM imaging head

(b) AR-PAM of a mouse's dorsal subcutaneous vessels[16]

(c) OR-PAM imaging head

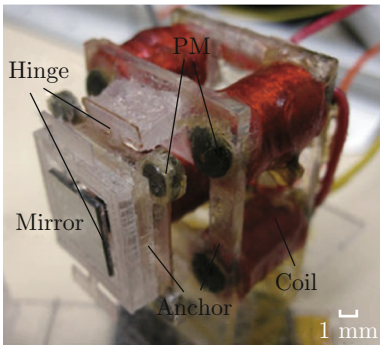
(d) OR-PAM of sO_2 in a mouse ear[18]

Fig. 1 AR-PAM and OR-PAM implementation and image

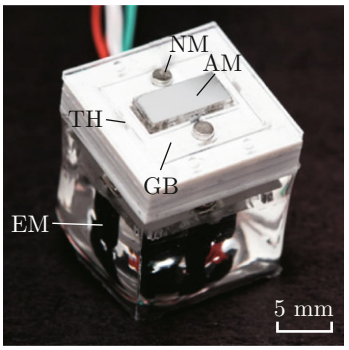
imaging head typically consists of a conical lens, a condenser and a focused transducer. The conical lens and the condenser can provide dark-field light illumination, and the focused transducer enables lateral resolution (tens to hundreds of μm). Figure 1(b) shows in vivo AR-PAM of a mouse's dorsal subcutaneous vessels[16], where a is the photoacoustic amplitude. However, an easy and fast operation of AR-PAM remains challenging due to the bulky components and low mechanical scanning speed. A potential solution is to use scanning mirror-based AR-PAM[17], which achieves fast scanning by circumventing the need for physical scanning of the imaging head. Synthetic aperture focusing technique can be further used to extend the depth of focus in AR-PAM[16-17]. For OR-PAM, the imaging head may comprise an objective, an optical-acoustic combiner and an ultrasonic transducer, as shown in Fig. 1(c). Like scanning AR-PAM, a motorized stage can be used for scanning[18]. Figure 1(d) shows OR-PAM of hemoglobin oxygen saturation (sO_2) in a mouse ear[18]. Alternatively, laser-scanning OR-PAM has been developed for fast scanning[15]. The ultrasonic transducer is kept stationary while the laser light is raster scanned by a galvanometer scanner. Data acquisition time of less than 2 min for 256 point × 256 point scanning can be achieved. Fast voice-coil scanning OR-PAM can achieve real-time B-scan imaging, 20 Hz over a 9 mm scanning range and 40 Hz over a 1 mm scanning range[19]. Individual red blood cells (RBCs) in capillaries were in vivo imaged in real time. Fully-motorized OR-PAM employs both the 2D galvanometer scanner and the 3D motorized stage, which enables five complementary scanning modes with high imaging speed and wide field of view[20]. The fully-motorized OR-PAM system is able to simultaneously quantify microvasculature diameter, sO_2 and blood flow. Thus, it has potential for measuring metabolic rate of oxygen. As can be seen, the advance of scanning PAM not only benefits the system's performance but also extends the scope of PAM applications.

1.2 MEMS Scanner Technology for Photoacoustic Microscopy

As mentioned above, scanning PAM performed with a two-axis motorized stage suffers from slow imaging speed and relatively bulky setup and thus is mainly suitable for tabletop operations. Small size imaging probe with fast imaging speed is crucial to facilitate preclinical and clinical applications of PAM. In the past few years, MEMS scanning mirrors have been widely developed[21-22]. They have small size and fast scanning speed and thus are a good choice of scanning components for constructing compact and hand-held imaging probes. MEMS scanning mirrors are first developed for steering optical beam in air. The MEMS scanner has been used in multiple medical imaging modalities such as optical coherence tomography[23], multi-photon microscopy[24] and confocal microscopy[25]. Besides, endoscopic imaging technology has been greatly advanced by making use of the MEMS scanner in numerous medical imaging applications[26]. However, for PAM and ultrasound microscopy, such MEMS scanner is not suitable because it cannot be operated in water which serves as the coupling medium for high-frequency acoustic waves. In order to address this issue, water-immersible or waterproof MEMS scanning mirrors have been developed later to make them workable in a water environment. A one-axis MEMS scanner was developed with a small form factor[27]. The scanner consisting of a mirror plate supported by polymer hinges and an electromagnetic microactuator is able to perform one-axis scanning of 12.1° at a resonance frequency of 210 Hz in water. The overall size of the scanner module is less than 7 mm × 5 mm × 7 mm. A two-axis MEMS scanner capable of 2D scanning was developed to acquire 3D images[28], as shown in Fig. 2(a). The scanner has electromagnetic microactuators to drive a silicon mirror plate. The fast axis has a resonance frequency of 164 Hz and a scanning angle of ±10° (AC driving) or ±12° (DC driving) in water operation, while the slow axis reaches a resonance frequency of 38 Hz and a scanning angle of ±6° (AC driving) or ±10° (DC driving) in water



(a) Water-immersible scanning mirror[28]



(b) Waterproof scanning mirror[29]

AM—Aluminum mirror, EM—Electromagnet,
NM—Neodymium magnet, GB—Gimbal,
PM—Permanent magnet, TH—Torsional hinge

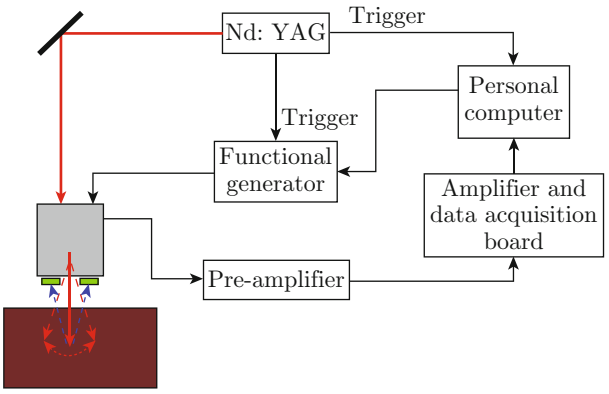
Fig. 2 Photographs of the two-axis MEMS scanning mirrors for PAM

operation. Another two-axis polydimethylsiloxane (PDMS) based waterproof scanner with a flexible structure was constructed[29], as shown in Fig. 2(b). The scanner size is 15 mm × 15 mm × 15 mm, and its maximum scanning angles are 18° and 13° for two axes, respectively, in water operation.

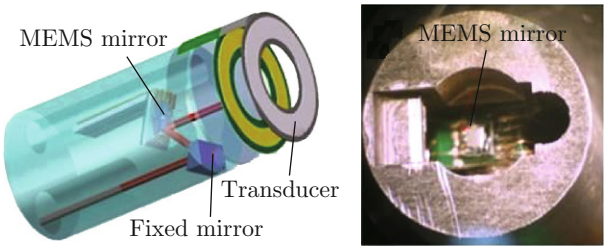
2 PAM by MEMS Scanner

2.1 AR-PAM by MEMS Scanner

Xi et al.[30] reported the first MEMS-based scanning photoacoustic imaging system, as shown in Fig. 3. In this system, the MEMS scanning mirror with an aperture size of 1 mm × 1 mm is used to scan unfocused light which passes through the hollow center of a ring-shaped polyvinylidene fluoride transducer with a central frequency of 2.5 MHz. The diameter of the probe is 11.5 mm. The probe has a lateral resolution of less than 0.7 mm and an axial resolution of less than 0.5 mm. Besides, the imaging depth up to 2.5 mm and the imaging area of 9 mm × 9 mm with 50 pixel × 50 pixel are achieved. Ex vivo imaging of small objects in tissue and in vivo imaging of blood vessels on a human hand were demonstrated. While it is promising in the first attempt, the probe needs to be optimized in several aspects such as increasing scanning speed, improving spatial resolution, and reducing the probe size for endoscopic applications.



(a) Schematic of the MEMS-based scanning photoacoustic imaging system

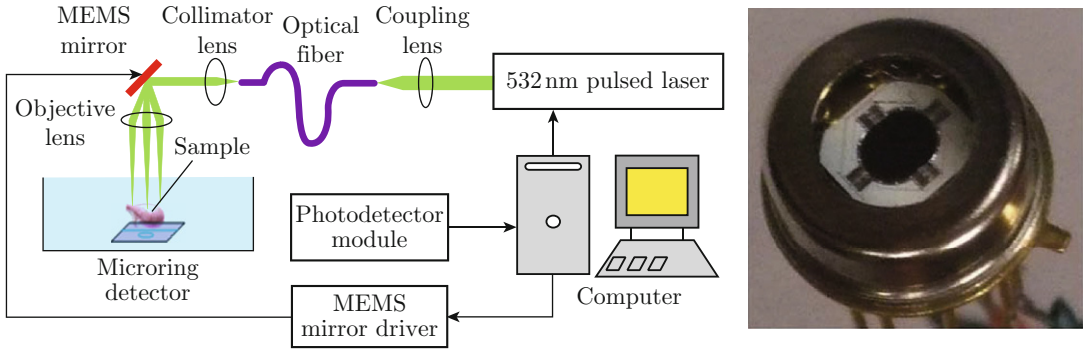


(b) 3D schematic of the probe (c) Photograph of the probe

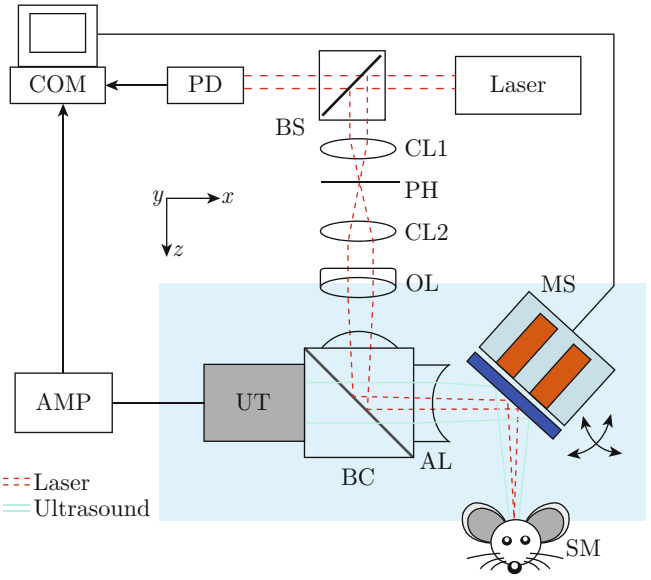
Fig. 3 MEMS-based AR-PAM[30]

2.2 OR-PAM by MEMS Scanner

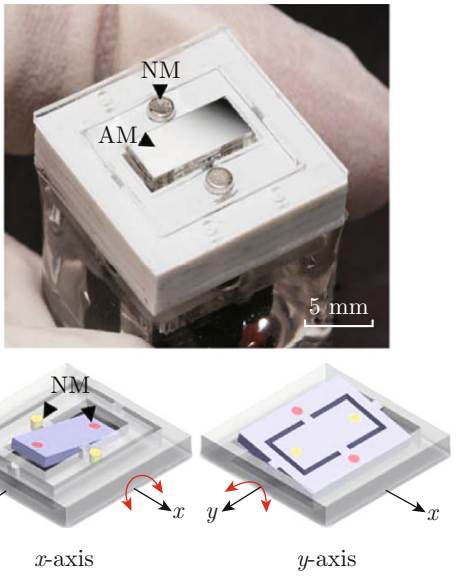
We developed a prototype of a miniature OR-PAM probe using a commercial MEMS scanner for the raster scan of the laser beam[31-32]. Besides, a microring resonator capable of broadband ultrasound detection was used for photoacoustic detection. A lateral resolution of 8.8 μm and an axial resolution of 19 μm are achieved. The schematic is shown in Fig. 4(a). The prototype is operated in transmission mode with the microring detector beneath the sample, which hampers in vivo imaging applications. A transparent microring may be used to enable reflection-mode PAM[33]. Yao et al.[34] implemented wide-field fast-scanning OR-PAM using the above-mentioned water-immersible MEMS scanning mirror. The optical and acoustic beams are confocally aligned by using an optical-acoustic beam combiner and are simultaneously steered by the MEMS scanner, which ensures uniform photoacoustic sensitivity with fast scanning. The MEMS mirror plate (size: 9 mm × 9 mm; thickness: 0.5 mm) was made of silicon with gold coating to provide good optical and acoustic reflection. Besides, the hinges to support the mirror plate were made of high-strength flexible materials to resist surface tension forces in water. The system has a lateral resolution of 2.4 μm and an axial resolution of about 26 μm. A B-scan imaging rate of 400 Hz over a 3 mm scanning range is achieved. Volumetric imaging is realized by scanning the MEMS mirror (fast axis) and the step motor (slow axis). By virtue of high imaging speed, the flow dynamics of RBCs and carbon particles in a mouse ear was imaged in vivo. The MEMS-based OR-PAM has potential for studying highly dynamic biological processes. A similar design with confocal configuration of the laser and acoustic beams can be used to maintain high sensitivity. Kim et al.[35] further demonstrated a two-axis waterproof MEMS scanner made of flexible PDMS for OR-PAM. Figure 4(b) shows the schematic of the system. As shown in Fig. 4(c), the MEMS scanner consists of a movable part of PDMS coated with a thin aluminum film. The scanning is torsionally actuated by electromagnetic forces. PDMS has low stiffness and is thus advantageous in reducing the required driving voltage. Moreover, by utilizing the high resistance and hydrophobic property of PDMS, it has the waterproof characteristic to avoid a short circuit in water. A wide 2D scanning range of 9 mm × 4 mm can be realized. The footprint of the MEMS scanner has a compact size of 15 mm × 15 mm × 15 mm. Similar spatial resolutions are achieved, 3.6 and 27.7 μm along the lateral and axial directions, respectively. For volumetric 3D imaging, a data acquisition rate of 0.25 Hz and an actual display rate of 0.14 Hz are demonstrated. The system is compact with fast imaging ability, which can be useful for clinical applications.



(a) Schematic of the MEMS-based OR-PAM system (left) and photography of the MEMS mirror (right)[31]



(b) Schematic of the two-axis waterproof MEMS-based OR-PAM system[35]



(c) Photograph and schematic of the MEMS mirror[35]

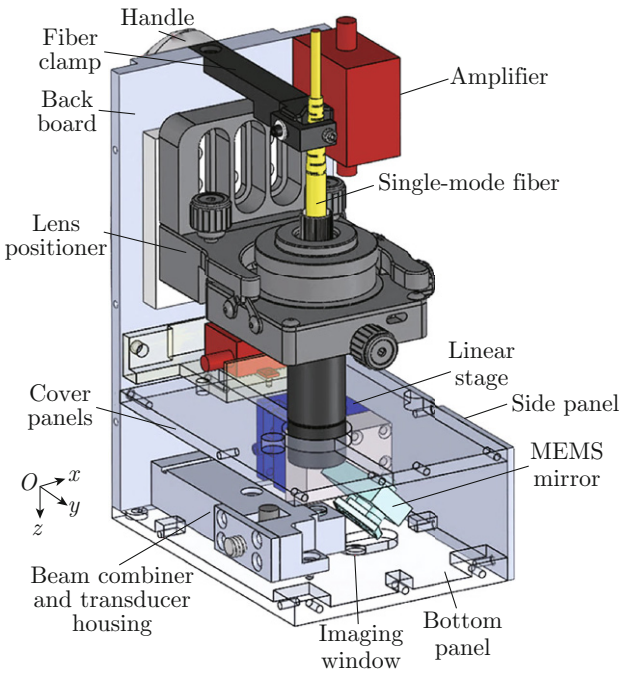
AL—Acoustic lens, AM—Aluminum mirror, AMP—Amplifier, BC—Beam combiner, BS—Beam splitter, CL—Condenser lens, COM—Computer, MS—MEMS scanner, NM—Neodymium magnet, OL—Objective lens, PD—Photodiode, PH—Pin hole, SM—Sample, UT—Ultrasonic transducer

Fig. 4 MEMS-based OR-PAM

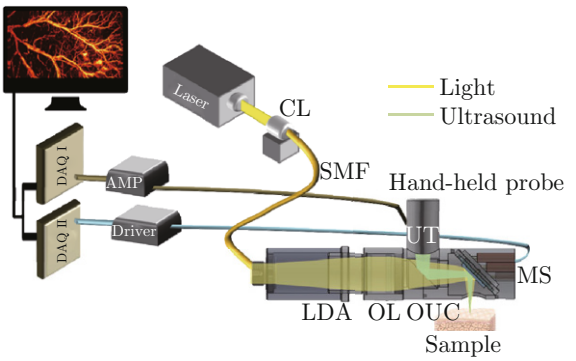
3 Derived Development

3.1 Hand-Held Miniature Probe

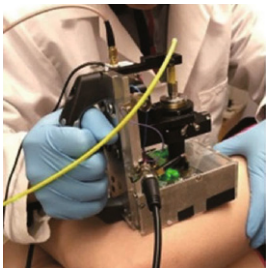
Figure 5 illustrates the hand-held PAM probe and image. Yang et al.[36] developed a miniature hand-held probe. A light beam with a spot size of 0.8 mm in diameter is delivered to the probe and scanned by the MEMS mirror. The probe has an axial resolution of 0.5 mm and a lateral resolution of 0.2—0.7 mm depending on the imaging depth. Lin et al.[37] demonstrated a compact hand-held OR-PAM probe capable of fast imaging, as shown in Fig. 5(a). On the basis of the work of utilizing the one-axis water-immersible MEMS scanner by Yao et al.[34], the group further developed a two-axis MEMS scanner with custom-designed housing to realize hand-held operation. The performance of the probe is 5 μm for the lateral resolution, 26 μm for the axial resolution, and 2 Hz for the 3D imaging rate over an imaging volume of 2.5 mm × 2.0 mm × 0.5 mm. The hand-held probe (dimensions: 80 mm × 115 mm × 150 mm) is able to perform OR-PAM more flexibly than conventional benchtop systems. For example, a volunteer's leg can be imaged by the probe, as shown in Fig. 5(c). Park et al.[38] reported a similar hand-held OR-PAM probe with a much smaller size, 17 mm in diameter, as shown in Fig. 5(b). The calibrated lateral resolution is 16 μm; the B-scan and volume imaging rates are 35 and 0.2 Hz (for 200 point × 700 point scanning), respectively. In vivo imaging of mouse ears, eyes and brains was demonstrated. Figure 5(d) shows photoacoustic maximum amplitude projection (MAP) image of a mouse eye.



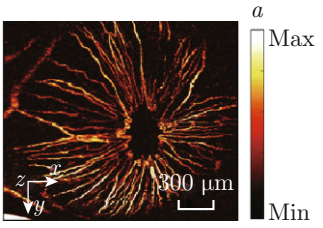
(a) 3D rendering of the hand-held OR-PAM probe[37]



(b) Schematic of the hand-held OR-PAM probe[38]



(c) Photograph of imaging of a volunteer's leg by the probe in (a)[37]



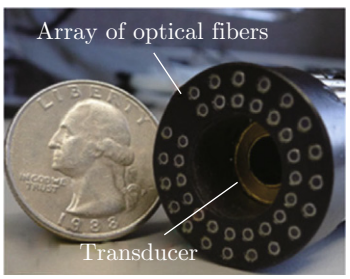
(d) Photoacoustic MAP image of a mouse eye[38]

LDA—Light delivery assembly, OUC—Opto-ultrasound combiner

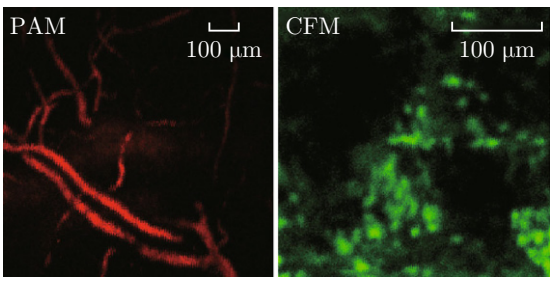
Fig. 5 Hand-held PAM probe and image

3.2 Dual-Modality Imaging

The MEMS scanner may be used to scan the laser beam for other imaging modalities, and thus another imaging modality can be integrated to provide additional information. Figure 6 illustrates the dual-modality imaging. Yang et al.[36] demonstrated a dual-modality probe integrating photoacoustic imaging and diffuse optical tomography (DOT). The MEMS scanner is used to scan both the pulsed laser for photoacoustic imaging and the continuous wave laser for DOT. As shown in Fig. 6(a), a ring-shaped transducer is used to detect photoacoustic signal for photoacoustic imaging, while an array of optical fibers placed along circular paths is used to collect diffused light for DOT. The probe can be applied to image-guided surgery, where DOT (resolution: 3—4 mm) can be used to identify the location and size of the tumors and photoacoustic imaging (resolution: 0.2—0.7 mm) can then be used to accurately visualize tumor margins. Integrating OR-PAM and confocal fluorescence microscopy (CFM), we proposed a prototype of a miniature probe[32]. The probe consists of a MEMS scanner, an objective lens and a microring resonator for ultrasound detection, as shown in Fig. 7. Lateral resolution for both OR-PAM and CFM was measured to be 8.8 μm; axial resolution of PAM and CMF was determined experimentally to be 19 and



(a) Photograph of the probe for PAM and DOT[36]



(b) PAM of a rat bladder (left) and CFM of a canine bladder (right)[32]

Fig. 6 Dual-modality imaging

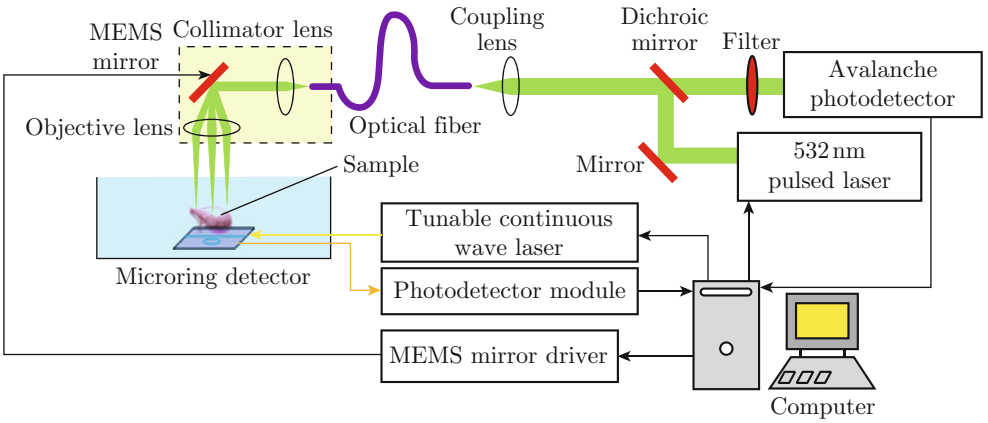
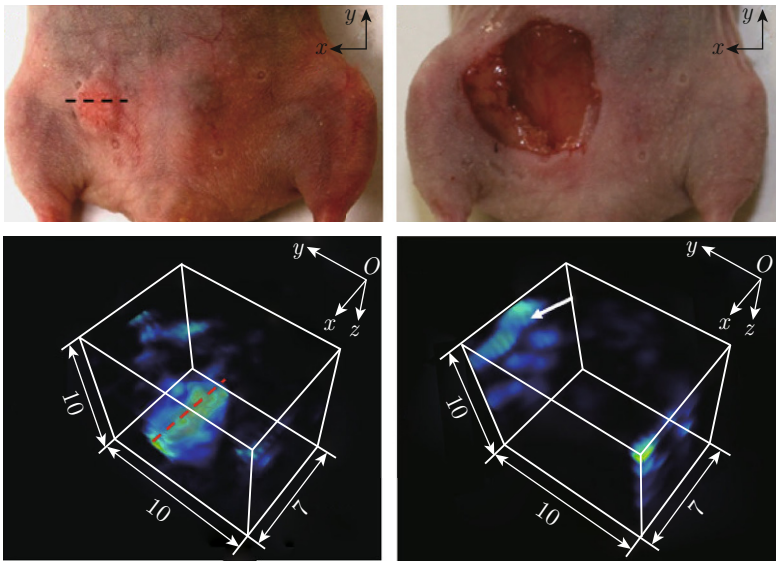


Fig. 7 Schematic of the imaging system for PAM and CFM[32]

53 μm, respectively. Equipped with dual contrasts, the probe is able to image not only microvasculature (absorption contrast) but also cellular structure (fluorescence contrast). Ex vivo imaging of animal bladder tissue was demonstrated, as shown in Fig. 6(b). The probe is mainly based on optical fibers and can be further developed and housed for in vivo endoscopic imaging applications. Other than the above two examples, other imaging modality based on point-by-point scanning, such as optical coherence tomography[39], may be integrated to the MEMS mirror-based PAM.

3.3 Novel Biomedical Applications

Xi et al.[40] demonstrated MEMS mirror-based photoacoustic imaging for intraoperative applications. In vivo 3D photoacoustic imaging of tumor implanted in the abdomen of a mouse before and after surgery was obtained, as shown in Fig. 8. Then, through accurate 3D map of the tumor, inspecting the completeness of tumor resection becomes possible. Besides, quantitative analysis of photoacoustic images was also demonstrated. The probe is small and thus can facilitate image-guided surgery applications such as resection of breast tumors. In order to facilitate in vivo and clinical applications, real-time imaging guidance is crucial and further improvement in the imaging speed of the probe is needed. Yao et al.[41] demonstrated high-speed functional PAM of a mouse brain in action. By using the MEMS scanner, a B-scan imaging rate of 400 Hz over about 3 mm scanning range and a 3D volumetric imaging rate of 1 Hz over 3 mm × 2 mm scanning area are achieved. In 3D imaging, fast-axis scanning is by the MEMS mirror and slow-axis scanning is by a motor. The PAM system was used to image the vascular morphology, blood flow, oxygenation and oxygen metabolism in the mouse brain at resting and stimulated stages. Figure 9 shows PAM of brain responses



(a) Before surgery (b) After surgery

Fig. 8 Photograph and 3D photoacoustic image of the mouse with a tumor implanted in the abdomen before and after surgery[40] (mm)

with electrical stimulations of mice. Fractional photoacoustic amplitude changes (shown in yellow) are superimposed on the vascular image (shown in red). Sequential photoacoustic excitation by using two consecutive laser pulses with a 500 ns delay between them was used to measure sO_2, which enables high-speed imaging of sO_2 as compared with the conventional dual-wavelength method[42]. The PAM is a highly complementary method to other imaging modalities in studying the mouse brain.

Finally, the properties and characteristics of the related published works are summarized in Table 1.

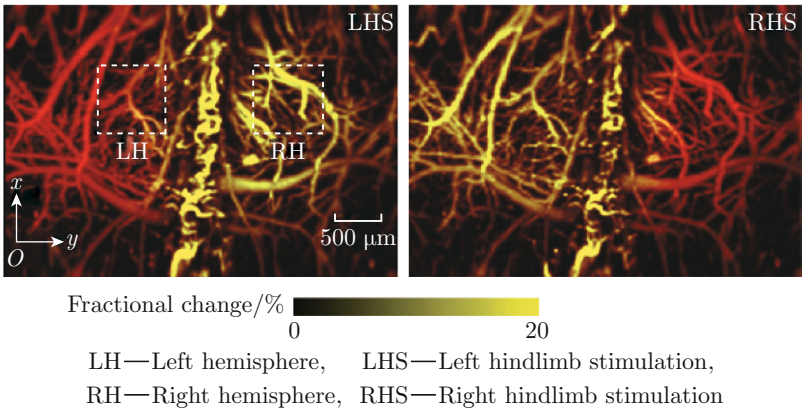


Fig. 9 PAM of brain responses with electrical stimulations of mice[41]

Table 1 Summary of PAM by MEMS scanner

Specialty	MEMS technology	Lateral resolution/μm	Special specification	Application	Source
Miniature probe	Electrothermal actuation	> 240	11.5 mm diameter	Intraoperative photoacoustic imaging	Refs. [30,40]
All optical	Electrostatic actuation	8.8	—	PAM and CFM, bladder imaging	Refs. [31-32]
Hand-held operation	Electrothermal actuation	> 200	25 mm diameter	PAM and DOT	Ref. [36]
Fast imaging	One-axis, water-immersible	2.4—3	400 Hz B-scan rate over 3 mm range	Functional PAM of mouse brain	Refs. [34,41]
	Two-axis, waterproof	3.6	0.25 Hz 3D PAM rate	—	Refs. [29,35]
Hand-held operation and fast imaging	Two-axis, water-immersible	5	80 mm × 115 mm × 150 mm dimensions, 2 Hz 3D PAM rate	PAM of human skin and leg	Ref. [37]
	Two-axis, waterproof	16	17 mm diameter, 0.2 Hz 3D PAM rate	PAM of mouse brain and eye	Ref. [38]

4 Conclusion

In this paper, the progress of MEMS scanning mirror-based photoacoustic imaging in various aspects is reviewed. The MEMS scanner has advantages in fast scanning and miniature size, which makes the MEMS scanner favorable to be employed in scanning photoacoustic imaging. It is essential to design and fabricate a particular MEMS scanner to well suit the needs

of PAM imaging. For example, development of the water-immersible or waterproof MEMS scanner facilitates easy integration of the scanner in OR-PAM. Furthermore, specialized design of the MEMS scanner for different imaging applications is also important due to achievable scanning angles, power requirements, scanning speed and size. It has been demonstrated that employing the MEMS scanner in PAM facilitates biomedical and clinical applications such as functional PAM of the mouse brain. Besides, MEMS mirror-based PAM has shown derived applications such as hand-held probes and dual-modality imaging. As the technologies continue to advance, we expect to see more powerful applications besides imaging, such as image-guided therapy and theranostics. Thus far, for MEMS mirror-based photoacoustic imaging in human, only imaging of a red mole on a volunteer's leg was demonstrated. More clinical studies will be needed in the future to bring the technology from laboratories to hospitals.

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