A THREE DIMENSIONAL REAL-TIME MEMS BASED OPTICAL BIOPSY SYSTEM FOR IN-VIVO CLINICAL IMAGING

Daniel T. McCormick[1], Woonggyu Jung[2,3], Yeh-Chan Ahn[2], Zhongping Chen[2,3] and Norman C. Tien[4]

[1]Advanced MEMS Inc., Berkeley, CA, USA
(Tel : +1-530-867-0905; E-mail: dmcc@advancedmems.com)
[2]Beckman Laser Institute, Irvine, CA, USA
[3]Department of Biomedical Engineering, University of California, Irvine, CA, USA
[4]Department of Electrical Engineering and Computer Science, Case Western Reserve University, Cleveland, OH, USA

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Abstract: In this work we present our latest "optical biopsy" system realized via MEMS based optical coherence tomography imaging. We report, for the first time, real-time 3-D optical biopsies of human internal organs employing a miniature MEMS based endoscopic probe in a clinical environment. We also present a variety of MEMS imaging probes, each designed for a particular application area. Leveraging the unique advantages of specific OCT systems with properly optimized MEMS probes we are able to achieve truly optimal results for individual clinical and research applications. Artifact free images with 5μm×5μm×5μm sampling resolution (10μm×10μm×10μm optical) at speeds of 33μs per voxel are achieved.

Keywords: micro-electromechanical systems (MEMS), bio-photonics, 3D imaging, optical coherence tomography (OCT), minimally invasive imaging, *in-vivo* imaging

I. INTRODUCTION

Optical coherence tomography (OCT) is an emerging imaging modality capable of achieving high resolution, cross-sectional images in tissue and other materials. [1]-[4] Due to the non-destructive nature of low-power optical imaging technologies biophotonics has become a major area of research focus in both academia and industry. In particular OCT has received a great deal of attention in the fields of biology and medicine. This is due, in part, to the fact that in addition to providing high resolution, non-destructive tomographic imaging capabilities OCT provides the opportunity to simultaneously realize real-time visualization of tissue structure and blood flow in a non-invasive, or minimally invasive, manner.

Currently imaging technologies such as ultrasound and Doppler ultrasound are employed to obtain minimally invasive, *in-vivo*, real-time images of tissue structure and blood flow profiles. However, the spatial resolution of these techniques is limited to approximately 100μm due to the relatively long wavelength of acoustics waves. OCT takes advantage of the short coherence length of broadband light sources in order to achieve cross-sectional images with micrometer (2-10μm) scale resolution. Due to the limited penetration depth of OCT systems in most biological tissue (approximately 2-3mm) miniaturized endoscopic probes are required for imaging of internal organs and tissue. Furthermore, small handheld probes with fast imaging speeds, excellent stability and ease of use are required for a wide range of clinical applications including ophthalmology and imaging of the skin as well as the oral cavity. Advances in silicon micromachining and micro-electromechanical systems (MEMS) technologies provide an enabling technology, allowing a new approach to be taken in order to achieve high-speed, high resolution OCT imaging. Modern photolithography and micromachining technologies allow the realization of structures and devices that are capable of manipulating light with sub-wavelength precision. The small physical size of MEMS optical components is highly advantageous when building miniaturized, portable scanning heads, hand-held scanners and

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minimally invasive endoscopic probes. In addition, MEMS technologies allow the realization of miniature optical systems exhibiting both high speed and low power operation.

A large number of MEMS based optical scanners have been developed since the inception of MEMS technologies; applications have ranged from the creation of micro-silicon optical benches and all-optical photonic switches to free space communication, displays, imaging and adaptive optics. MEMS mirrors and scanning lenses have previously been employed to provide beam steering in biophotonic applications such as confocal microscopy [5], cell sorting [6] and florescence imaging [7]. Recently MEMS devices have also been developed for OCT applications and OCT systems utilizing a scanning MEMS device in the sampling arm have been presented [8]-[10]. Previously we demonstrated the first three-dimensional (3-D), high-resolution, video rate capable, MEMS based OCT system. [11] High speed, 3-D OCT provides several improvements and advantages compared to 2-D imaging. The ability to arbitrarily visualize and manipulate 3-D images of tissue containing lesions and tumors provides significant additional diagnostic information to both physicians and researchers. In this paper we present a fully-functional, clinical OCT system complete with a wide range of application specific, optimized probes for real-time, 3-D, in-vivo and in-vitro imaging.

II. OCT System and Methods

A schematic diagram of a simplified 3D Time-Domain OCT system is provided in Fig. 1. Light from a low coherence source (in this work the source wavelength is 1310nm with a 70nm bandwidth at a power level of 10mW) is coupled into a fiber-optic Michelson interferometer. A visible aiming beam (typically a 633nm laser) is also coupled into the interferometer in order to allow simultaneous imaging and visual identification of the area of tissue being imaged. This is useful during general clinical imaging as well as for precise labeling of areas to be identified for post OCT histologies.

In the reference arm of the interferometer a rapid scanning optical delay line (RSOD) is utilized to provide a variable optical path length. In the time-domain (TD-OCT) system the RSOD line utilizes a galvanometer to scan a grating, allowing separate control of the phase and group delays. In addition, an electro-optical phase modulator is incorporated into the reference arm to generate a stable carrier frequency.

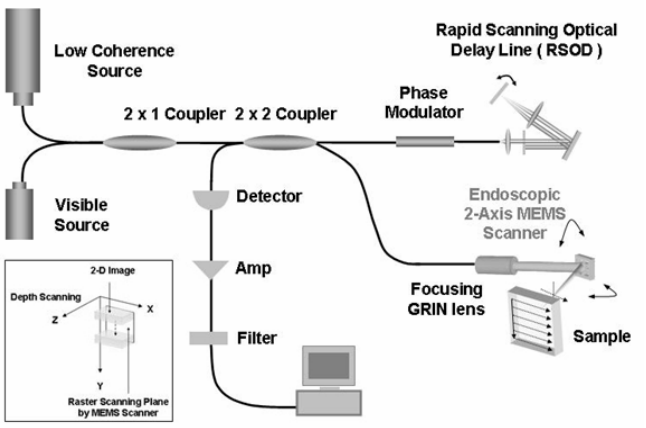

Fig.1. A simplified schematic diagram of the 3-D time-domain OCT system employing a 2-D scanning endoscopic probe.

The MEMS based probe is placed at the end of the sampling arm of the interferometer. The MEMS scan-head is used to direct a focused beam onto the sample as well as to provide beam scanning during image acquisition. In the presented schematic (Fig. 1) the MEMS scanner is illustrated with a pre-scan lens. In many bench-top and hand-held probes both pre-scan and post-scan optics are employed. However, in the case of endoscopic probes generally either a single pre-scan lens or lenslet is utilized. A 1-dimensional scanning device will allow a single cross-sectional (i.e. 2-D) image to be collected whereas a 2-dimensional or 2-axis scanning probe allows 3-D images to be obtained.

The reflected beam entering the sample arm of the interferometer is recombined with the beam from the reference path and the interference signal is detected using a high speed photodetector. The sampled signal is then processed and displayed as an image to the operator.

As previously described the MEMS based imaging probe serves as a means of delivering light to the sample being imaged as well as a beam steering and optical focusing device. The optical

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elements in the probe determine the lateral resolutions of the imaging system while the coherence length of the source determines the axial (depth) resolution.

III. MEMS Probe Design

When designing the MEMS devices and imaging probes numerous trade-offs are made between probe size, imaging speed, achievable resolution and ultimately cost. It is essential to identify the goals, requirements and preferences of clinicians as well as the source of design limitations in order to optimize each probe for a given application. Furthermore, ease of use and reliability are two important concerns when designing the probes for clinical use. Finally, patient safety is the primary concern during design.

The optical performance of the MEMS scanner must be sufficient as not to degrade the overall image quality. In general a scanner that achieves the largest angle and the highest operating speed is desirable. Minimum clinical line scan lengths range from approximately 1mm to 2mm for most applications. Imaging speed is a very important parameter if large areas are to be imaged quickly and also in order to minimize motion artifacts.

In addition, for a mirror based scanner the aperture size and quality are also very important parameters. In order to maximize resolution the objective is to achieve a larger mirror. However, as the mirror is enlarged the inertia of the mirror is increased and for a given spring stiffness the resonant frequency will decrease. On the other hand if the suspension is stiffened to maintain a given speed the torque available from the actuator must be increased. For a given fabrication technology and set of critical-dimensions this equates to enlarging the size of the actuator and thereby the area occupied by the die and package. The mirror must have good reflectivity in the visible and near infrared ranges; this requires either metallization or a dielectric mirror. The mirror surface should be sufficiently flat (generally $r_{curvature} \geq 1m$) as to not distort the beam and must also have surface roughness less than 100nm at a minimum.

It is also critical that the devices exhibit excellent accuracy and precision in terms of pointing stability and scan to scan repeatability. In our experience the angular accuracy must be, at a minimum, better than one percent of the angle step size.

In some cases it is desirable to achieve maximum optical resolution; in others higher acquisition rates or larger fields of view are required. Many parameters of the MEMS device and optical probe must be selected during design, fabrication or assembly. Others can be adjusted on a case-by-case basis before an imaging session (this require recalibration). However, using our MEMS control system it is possible to adjust many operating parameters, such as scan mode (point-to-point or constant velocity), scan region, scan speed and sampling resolution, in real-time. Therefore, the clinician can select the best probe for a specific application and still make trade-offs between field-of-view, image resolution and acquisition speed continuously during an imaging session.

The MEMS scanning actuators employed in this work are monolithic, single crystal silicon, 2-dimensional, gimbal-less, vertical comb-driven structures. The devices are designed and realized in a self-aligned DRIE fabrication process on SOI [12],[13]; for endoscopic packaging the area footprint of the die is 2.8mm × 3.3mm. The mirrors are fabricated in a separate SOI process and metalized prior to being bonded to the actuator. This design approach allows the mirror and actuator to be independently optimized.

An SEM and optical micrographs of scanners with bonded mirrors are presented in Fig. 2.

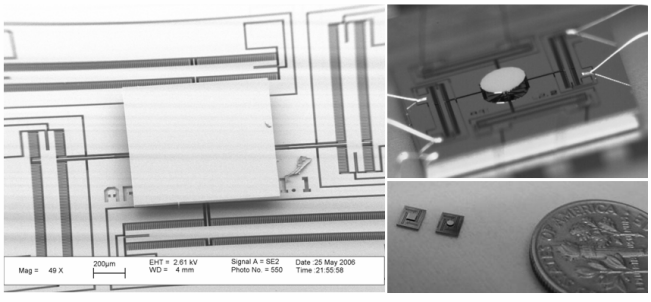

Fig. 2. (left) SEM of an endoscopic scanner, the die is 2.8mm×3.3mm with a 1mm bonded mirror. (top right) A micrograph of a larger die and 800μm mirror. (bottom right) Scanners with different mirror apertures and a US dime for size reference.

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The apertures used in this work are metalized, low-inertia, SCS structures with a thinned mirror plate (1.5-5µm), thick stiffening trusses (~20µm) and a standoff pedestal (~120µm). A variety of scanners with 800µm, 1mm, 1.2mm, 1.6mm and 2.0mm mirror diameters have been realized.

The mirrors and optical components are integrated into bio-compatible packages which provide optical alignment, electrical connections, mechanical protection and optical windows. The precise design of the package depends on the specific application. In this work four generations of endoscopic probes ranging in diameter from 3.9mm to 5.5mm have been utilized. Handheld probes with an outer diameter of 10mm and 15mm are also reported.

Fig. 3 provides photographs of fully functional 1st, 2nd and 4th generation endoscopic probes (3.9mm, 4.9mm and 5.0mm respectively.)

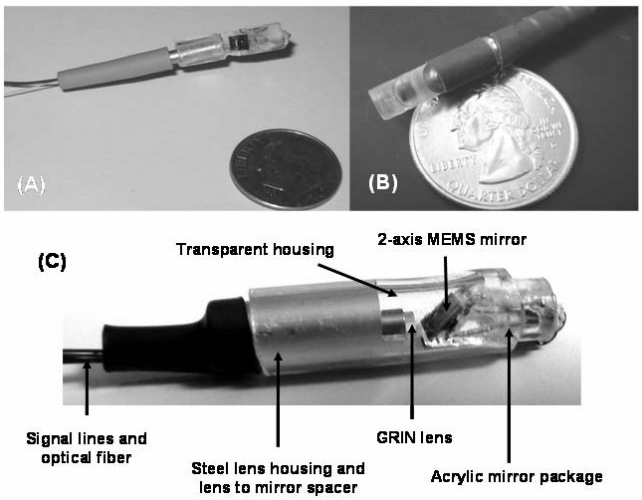

Fig. 3. Photographs of completed fully-functional probes. (A, B) 1st (3.9mm) and 4th (5.0mm) generation probes are compared to a US dime and a US quarter respectively. (C) Magnified photograph of 2nd generation probes. The steel lens housing provides rigid as well as proper alignment with and spacing to the MEMS device; the outer diameter of this probe is 4.9 mm.

IV. Image Acquisition and Results

Employing the MEMS based optical biopsy system large numbers of *in-vivo* and *in-vitro* image sets have been collected of healthy and diseased tissue. Clinical *in-vivo* imaging has been performed in both animals and humans.

The normal imaging mode for our clinical OCT system is to display 2-D cross-sectional images to the clinician on a monitor in real-time during a scan. The imaging frame rate is dependant on many factors, including the number of voxels in the image and the speed of the OCT hardware. There may also be a difference between the acquisition speed and the display rate as the clinician or physician may wish to slow down the visualization on the monitor. Therefore it is not meaningful to quote frame rates without describing the specific imaging conditions. In the presented experiments all imaging speeds are limited by the axial scanning rate or processing hardware, not the speed of the MEMS device. For the TD-OCT system the axial scan rate is 500Hz, while for frequency domain system rates as high as 40kHz are achievable. In a point-to-point scanning mode imaging times of 33 microseconds per point are achieved, and in constant velocity modes 4000 lateral scans per second are realized.

The typical optical resolutions of our probes is between 10µm × 10µm × 10µm and 20µm × 20µm × 10µm and the imaged volumes nominally range from 1mm × 1mm × 1.4mm to 2mm × 2mm × 1.4mm.

A standard endoscopic instrument and fiber based camera are used to guide the positioning of the OCT probe during imaging experiments. This allows surgeons and clinicians already familiar with standard biopsy and endoscopic tools to quickly become comfortable and proficient with the OCT biopsy system. Fig. 4 presents images of a probe prepared for esophageal imaging and a picture of the probe scanning the upper airways of a human patient.

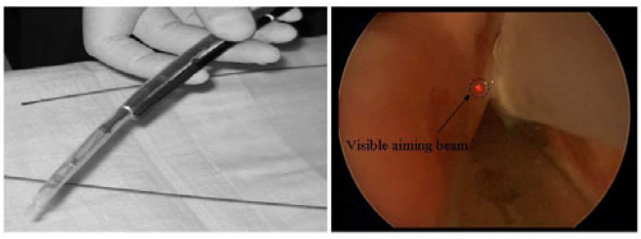

Fig. 4. (left) A 4th generation MEMS probe attached to a flexible fiber-optic bronchoscope. (right) An image from the endoscope camera of a MEMS optical biopsy probe in the upper airway of a human patient. The endoscope guides the positioning of the MEMS probe and the visible aiming beam allows precise identification of the imaged area.

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In Fig. 5 *in-vivo* OCT images of healthy esophageal and rectal tissue collected from an anesthetized rabbit utilizing 4th generation endoscopic probes and a spectral domain OCT (SD-OCT) system during clinical studies are presented. The optical resolution of these images is 20µm × 20µm × 10µm and the imaged volume is 1mm × 1mm × 1.4mm. At this resolution and scan volume the frame rate of the SD-OCT is approximately 8 frames per second. These images clearly show the important structural and morphological features of the tissue. Histologies of the imaged tissue taken to verify the OCT images are also presented in Fig. 5.

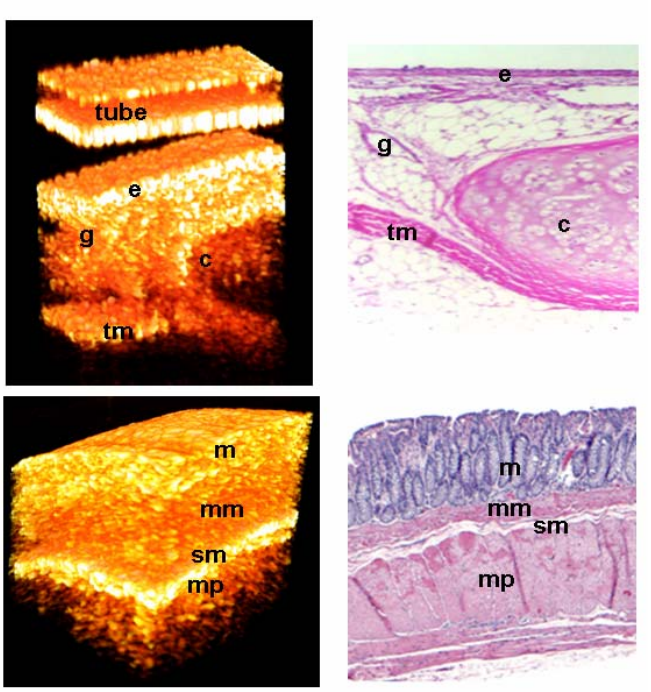

Fig. 5. (top) An in-vivo OCT image and subsequent histology of healthy rabbit trachea, clearly visualizing the epithelium (e), glands (g), cartilage (c) and tunica muscularis (tm). (bottom) In-vivo OCT image of healthy rabbit rectal tissue showing the important structural features.

Clinical studies have also been completed with human patients. In addition to providing the ability to image large regions of tissue in a short period of time it is also possible to image organs and tissue that can be permanently damaged by traditional excissional biopsies, such as the vocal chords.

For imaging of the human vocal chords the optical biopsy probe is attached to a rigid telescope type endoscope, which provides direct visualization of the region to be imaged and also allows precise positioning of the probe. Utilizing this setup 3-D *in-vivo* images were obtained of the laryngeal surface of the epiglottis as well as the false and true vocal cords under endoscopic visualization. A volume image of the true vocal chords is presented in Fig. 6. If it is determined that a lesion must be removed the optical biopsy system enables precise identification of resection boundaries.

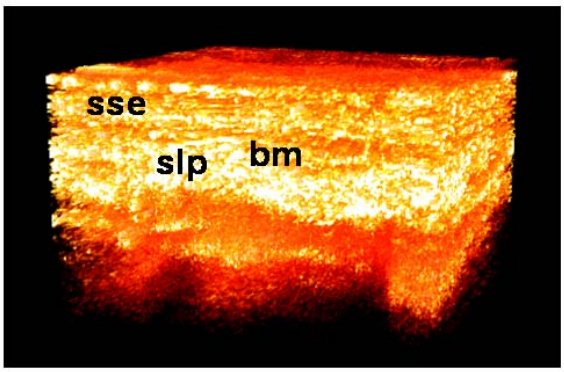

Fig. 6. True vocal cord of human in-vivo. Important structures such as the stratified squamous epithelium (sse), basement membra (bm), and superficial lamina propria (slp) are clearly visualized.

Employing a hand-held probe *in-vivo* images of human skin have also been obtained and important features such as the epithelial layer, epidermal layer and sweat ducts are clearly visualized. In Fig. 7. a 3-D image of human skin tissue is shown.

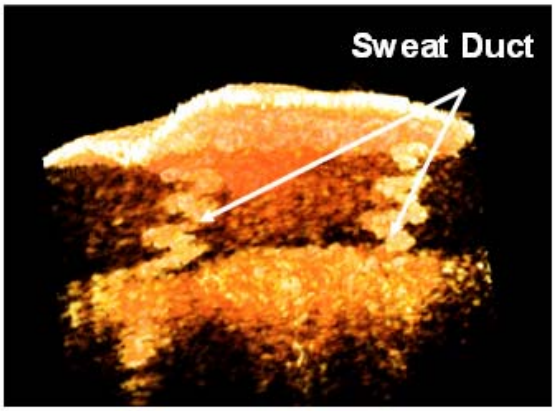

Fig. 7. In-vivo image of a human finger, the image has been thresholded to clearly show the spiral structure of the sweat ducts.

The presented image was obtained with the SD-OCT system and has been thresholded to emphasize the spiral structure of the sweat ducts,

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which are approximately 20-40µm in diameter. False coloring can also readily be applied during post-scan image processing in order to simultaneously emphasize various structures of different optical density in the tissue.

V. CONCLUSION

We have realized a 3-D MEMS based OCT optical biopsy system capable of providing real-time volume images with optical resolutions of 20µm or less both *in-vitro* and *in-vivo*. Bench-top, handheld and endoscopic probes have been employed to image healthy and diseased tissue in clinical studies with animal as well as human subjects. Previously the system has also been used to diagnose early stage cancer in an animal model.

It is believed that this optical biopsy system will find use, and have significant impact, in a wide range of clinical and research environments.

As neither the speed limits nor the optical resolution limits of our MEMS devices have been reached we will continue to develop faster imaging systems with higher resolution capabilities. We are also continuing to work with physicians and clinicians to optimize individual imaging probes for use in a variety of specific applications.

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