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Review

MEMS based fiber optical microendoscopes

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ABSTRACT

Fiber-optical microendoscopy has recently been an essential medical diagnostic tool for patients in investigating tissues *in vivo* due to affordable cost, high quality imaging performance, compact size, high-speed imaging, and flexible movement. Microelectromechanical systems (MEMS) scanner technology has been playing a key role in shaping the miniaturization and enabling high-speed imaging of fiber-optical microendoscopy for over 20 years. In this article, both review of MEMS based fiber-optical microendoscopy for optical coherence tomography, confocal, and two-photon imaging will be discussed. These advanced optical endoscopic imaging modalities provide cellular and molecular features with deep tissue penetration enabling guided resections and early cancer assessment.

Contents

1. Introduction

One of the major public health problems in human history is the Cancer disease killing over 7 million people each year [1]. Currently, the clinical diagnosis of most cancers and their precursors is based on gross structural features obtained from biopsy

Abbreviations: US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; NIR, near infrared; NA, numerical aperture; WD, working distance; UV, ultraviolet; FOV, field of view; SAC, single-axis confocal; DAC, dual-axis confocal; MEMS, microelectromechanical systems; CM, confocal microscopy; OCT, optical coherence tomography; 2P, two-photon.

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procedures, such as extent of local invasion, the presence of enlarged regional lymph nodes, and detection of lesions (>1 cm) in organs [2]. While this biopsy process has been the standard of care, it has many disadvantages, such as long diagnosis time, invasiveness, artifacts, sampling error, time consumption, relatively high cost, and interpretive variability. Therefore, the understanding of the underlying fundamental system biology is less explored due to the technical limits. It is not until 1895 that the scientific and medical communities are forever in debt to an accidental discovery of X-rays made by a German physicist Wilhelm Conrad Röntgen. Afterward, many noninvasive imaging modalities based on variety physical properties such as ultrasound (US), computed tomography (CT), and magnetic resonance imager (MRI) have been invented to perform disease analysis, diagnosis, prognosis, staging, treatment, and follow-up [3]. Even though, the above modalities are useful for delineating the deep extent of advanced carcinomas, they are insensitive to detect small, earlier intraepithelial lesions, which are more readily cured [4]. In contrast to the above modalities, optical imaging of tissue can be carried out noninvasively in real-time and *in vivo*, yielding high spatial resolution (submicron to micron scale). Moreover, the optical imaging modalities are inexpensive, robust, and portable because of advances in computing, optical fiber, semiconductor, and microelectromechanical systems (MEMS) technologies [5–7]. Current imaging modalities used in fiber optical microendoscopy include: optical coherence tomography (OCT) [8–10], confocal microscopy (CM) [11–13], and two-photon (2P) microscopy [14–16]. Those imaging modalities are often combined with the development of contrast agents targeting cancerous receptors enhancing accurate cancer detection [17,18]. Typically, MEMS technology has been integrated at the distal end as a scanning element with either raster scanning, random access, or lissajous scanning mode inside these microendoscopy to achieve two-dimensional (2D) *en face* scan imaging. Some of the advantages are fast speed (kHz-MHz), small in size (a few millimeters scale), low to medium power consumption, ease of integration, batch fabrication, and low cost. Sections below will briefly introduce each optical imaging modality, and its fiber optical endoscopic version based on MEMS scanner technology.

2. Optical microscopy

2.1. Optical coherence tomography

OCT was first demonstrated in early 1990s [8]. Since then, numerous applications of OCT for both biomedical and materials applications have emerged. At the same time, the resolution and capabilities of OCT technology have improved dramatically. OCT is the optical analog of US which can perform micron-scale resolution, cross-sectional tomographic imaging of the internal microstructure in materials and biological systems. OCT performs imaging by measuring the magnitude and echo time delay of backscattered light. In the standard embodiment of OCT imaging, an incident light beam is directed at the object to be imaged, and the time delay and magnitude of backscattered or backreflected light is measured in the axial or longitudinal direction. The beam is scanned in the transverse direction, and rapid successive axial measurements are performed, as shown in Fig. 1a. The result is a 2D data set, which represents the optical reflection or backscattering in a cross-sectional plane through the material or tissue. Frequency domain OCT employs a Michelson interferometer. The input light from a broadband frequency sweeping light source is divided into the reference arm and sample arm. The light beams on both arms are reflected back and form an interference signal at one port of the beam splitter. This interference signal is read by a photodetector and provides the depth information of the sample through inverse Fourier transform. By using the short coherence length of a broadband light source, the resolution of OCT can reach 1–15 μm depending on the light source employed, shown in Fig. 1b. The penetration depth of OCT is normally 1–3 mm, which is sufficient to image the depth of the epithelial layer, where most cancers are originated.

2.2. Confocal microscopy

CM concept was first introduced by Marvin Minsky in the 1957 when he was a postdoctoral fellow at Harvard University [11]. The modality uses linear light-tissue interactions to generate high image contrast with micron-scale resolution [11–13]. The principal advantage of CM is its ability to record section information of three-dimensional (3D) tissue data with cellular definition by rejecting out of focus light from its unique optical sectioning property via a pinhole (Fig. 2a). The achievable field of view (FOV) of CM is typically limited (<100 μm^2) and it requires the use of exogenous fluorophores to enhance image contrast. In standard operation, CM can be employed in two imaging modes namely reflectance and fluorescence. The former relies on the backscattered light from within the tissue and provide structural and anatomical information of cells and tissues whereas the latter records light generated by fluorescence contrast agents that target specific microstructures and has high sensibility and specificity. Fluorescence signal from linear light-tissue interaction is produced when a single excitation photon in the ultraviolet (UV) or visible regime is absorbed by electrons in tissue biomolecules that then transition into higher-energy (excited-state) levels. The electrons emit visible fluorescence photons when it spontaneously relaxes to the ground state, as shown in Fig. 2b. In this process, the fluorescence intensity (F)

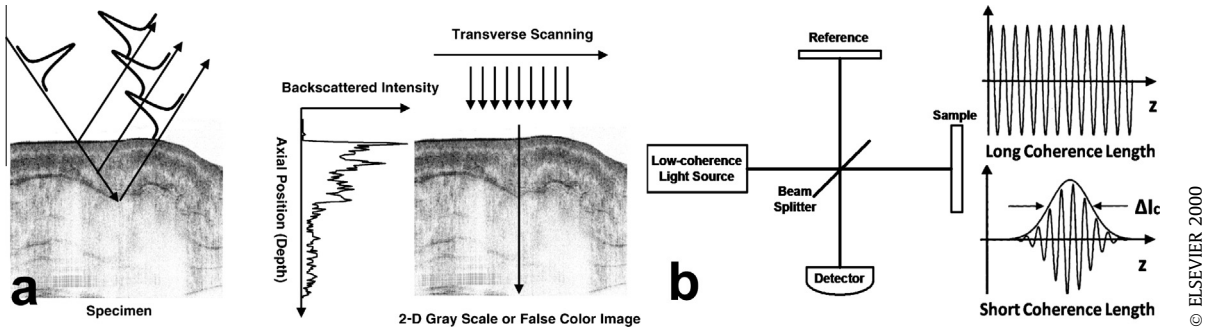

Fig. 1. (a) OCT generates cross-sectional images by performing measurements of the echo time delay of light at different transverse positions. The result is a 2D data set representing the backscattering in a cross-sectional plane of the tissue. Used with permission. (b) OCT working principle based on Michelson-type interferometer. The configuration measures the echo time delay of reflected light by using low-coherence interferometry. Reflections or backscattering from the object being imaged are correlated with light travelling through a reference path.