

Optical biopsy and imaging using optical coherence tomography

JAMES G. FUJIMOTO¹, MARK E. BREZINSKI^{2,4}, GUILLERMO J. TEARNEY¹, STEPHEN A. BOPPART¹,
BRETT BOUMA¹, MICHAEL R. HEE¹, JAMES F. SOUTHERN^{3,4} & ERIC A. SWANSON⁵

¹Department of Electrical Engineering and Computer Science Research Laboratory of Electronics, 30 Vassar Street, Massachusetts Institute of Technology (MIT), Cambridge, Massachusetts 02139, USA

²Cardiac Unit and ³Pathology Department, Massachusetts General Hospital, Fruit Street, Boston, Massachusetts 02114, USA

⁴Harvard Medical School, Fruit Street, Boston, Massachusetts 02114, USA

⁵MIT Lincoln Laboratory, 244 Wood Street, Lexington, Massachusetts 02173, USA

Correspondence should be addressed to J.G.F.

Medical imaging technologies can improve both the diagnosis and the clinical management of disease. Imaging modalities such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are examples of technologies that emerged from physical science and engineering but have had a significant impact in medical research and clinical practice. Each of these imaging modalities operates along different fundamental principles and thus affords the researcher or clinician complementary diagnostic capabilities.

Optical coherence tomography (OCT) is a new imaging technology that can provide micrometre-scale, cross-sectional images in biological systems^{1,2}. The technique is somewhat analogous to ultrasound B-mode imaging or radar, except that it uses light rather than sound or radio waves. Because OCT is an optical imaging technique, it can achieve spatial resolutions of 10 μm or less, approximately ten times as high as conventional ultrasound. In addition, unlike ultrasound, OCT does not require direct contact with the tissue being imaged. Because light is strongly scattered in most tissues, the imaging depth of OCT is limited to a few millimetres, and thus imaging of structures deep in the body is not possible. However, a wide range of tissues can be accessible directly or by catheter or by use of an endoscope.

The ultra-high resolution imaging capabilities of OCT can provide diagnostic information on tissue microstructure that cannot be obtained using other imaging modalities. Morphological information on tissues can, of course, be obtained by conventional biopsy and histopathology. However, excision of a tissue specimen is often contraindicated

or impossible. OCT has the potential to function as a type of 'optical biopsy' where morphology may be assessed using direct, real-time, catheter or endoscopic imaging *in situ*, without the need for excision.

The technology of OCT

Optical coherence tomography performs micrometre-scale, cross-sectional imaging of tissue structure in biological systems by directing a focused beam of light at the tissue to be imaged, then measuring the echo delay time for the light to be reflected from different microstructural features in the tissue. A cross-sectional image is constructed by scanning the light beam in the transverse direction on the tissue. The result is a micrometre-scale, cross-sectional image through the tissue, which somewhat resembles a histological section.

Optical coherence tomography imaging is based on a classical optical measurement technique known as low coherence (or white light) interferometry, which was in fact first described by Sir Isaac Newton. Low coherence interferometry has been used in optics to perform high precision measurements in optical fibres and optical components³⁻⁵. One of the first applications of low coherence interferometry to biological systems was pioneered by Fercher *et al.* for high precision measurements of axial eye length and corneal thickness^{6,7}. Low coherence interferometry is analogous to ultrasound A mode or axial mode measurement. Optical coherence tomography is a powerful extension of the optical ranging concept, which permits the measurement of two-dimensional, cross-sectional images with micrometre resolution^{1,2}.

A schematic of the OCT measurement system is shown in Fig. 1. The OCT system uses fibre optics and a compact

diode light source. The system is similar to a Michelson-type interferometer. Light from the source is split evenly via an optical fibre splitter, which functions as the interferometer. One of the fibres directs light to the tissue being imaged and the other fibre to a moving reference mirror. The distal end of the optical fibre can be integrated to a catheter or endoscope. The position of the reference

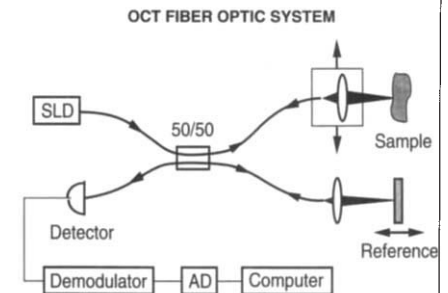


Fig. 1 Schematic diagram of optical coherence tomography imaging (OCT) system. The OCT system uses fibre optics and a compact diode light source. The light source is coupled into a fibre splitter, which functions like a Michelson-type interferometer. One of the fibres directs light to the tissue being imaged and the other to a moving reference mirror. By using a low coherence length light source and measuring the interference between light backscattered from the tissue and from the reference mirror, this distance and magnitude of optical scattering within the tissue can be measured with micrometre-scale precision. A cross-sectional image is produced by scanning the light beam across the tissue while the axial reflectance profiles at each transverse position are recorded by computer. The result is a two-dimensional representation of the optical backscattering of the tissue in cross section, which is displayed as a grey-scale or false-colour image.

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mirror is precisely controlled by system electronics and a computer. The light signal reflected from the tissue and light reflected from the reference mirror are recombined and interference between two light signals occurs only when their path lengths match to within coherence length of the light. This allows a precise (micrometre scale) determination of both the distance within the tissue from which the light was reflected or backscattered as well as its magnitude. The axial resolution of OCT imaging is determined by the coherence length of the light that is used for the measurement. For a typical OCT system that uses a compact super-luminescent diode light source, the axial resolution is 10 to 20 μm . If alternate light sources, such as ultra-short pulse lasers are used, the axial resolution may be improved to be 2 to 4 μm ^{8,9}.

A measurement performed with the light beam incident on a single point on the tissue yields a measurement of the variation in optical reflection or backscattering along the axis of the beam. A cross-sectional image is produced in a manner similar to radar: the light beam is scanned across the tissue, and the axial reflectance profiles at several transverse positions are recorded by computer. The result is a two-dimensional representation of the optical backscattering of the tissue in cross section. This can then be displayed as a grey-scale or false-colour image. Typically, the log of the magnitude of the optical backscattering is displayed according to a false-colour or grey-scale table. Examples of OCT images of atherosclerotic plaque in human aorta and glandular structure in human trachea *in vitro* are shown in Figs 2 and 3.

Potential applications

Optical coherence tomography is especially suited for diagnostic imaging in ophthalmology because the eye is transparent and provides optical access to both the anterior chamber as well as the retina^{2,10,11}. In contrast to direct visualization of the retina in conventional ophthalmoscopic fundus examination, OCT provides a cross-sectional tomographic view. Studies performed by Puliafito *et al.* demonstrate that OCT is a powerful diagnostic tool for a wide range of retinal diseases^{12,13}. It provides non-invasive, cross-sectional images of retinal lesions and microstructural changes with a resolution that cannot be achieved by any other imaging modality. Conditions such as macular holes, macular oedema, age-

related macular degeneration and glaucoma can be monitored using OCT. Preliminary clinical studies are currently under way to investigate the application of OCT for diagnosis and monitoring of these diseases.

Perhaps one of the most challenging and significant future applications for OCT is the possibility of developing 'optical biopsy' techniques for tissues other than the eye that are not optically transparent. Optical imaging in these tissues has traditionally been an extremely challenging problem. A key issue that must be addressed in order to develop such applications are limitations to the imaging depth and the mechanisms of image contrast between different tissues.

As OCT is an optical imaging modality, it relies on the penetration and backscattering of light into tissue to construct cross-sectional, tomographic images. Although tissue appears relatively opaque for visible light wavelengths, it is in fact relatively non-absorbing at wavelengths of light in the near infrared. The dominant process that limits imaging depth in OCT is optical scattering rather than absorption. Scattering limits imaging depth because it causes attenuation of the light as well as randomization of image information¹⁴⁻¹⁶. However, scattering of light is strongly dependent on wavelength, and thus use of optimized wavelengths (1,300 nm) can achieve imaging depths of 1 to 2 mm in most tissues. Although this is shallow compared to other modalities such as ultrasound, MRI or CT, it is sufficient for many clinical diagnostic applications that are based on *in vivo* catheter or endoscopic delivery, as well as for research or pathology applications where direct access to tissue *in vitro* is possible.

One of the main areas that we are currently investigating is the use of OCT for intravascular imaging. This is a clinically significant example of a diagnostic situation where catheter-based, non-excisional determination of pathology can have a significant impact on diagnosis and clinical management. It is also a model application for a wide range of optical biopsy scenarios. Recent studies have shown that the morphology of atherosclerotic plaques are an important predictor of myocardial infarction¹⁷⁻²¹. In particular, the plaques that are cholesterol laden and have a lipid core are prone to rupture and result in a sequence of events that leads to acute thrombosis. Conventional angiographic imaging techniques can indicate vessel

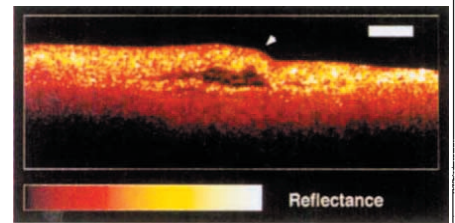


Fig. 2 An OCT image of an atherosclerotic human aorta *in vitro*. A small, intramural collection of lipid and matrix is present deep within the thickened intimal wall (arrow). Bar, 500 μm . The image was acquired using a 1,300-nm light source and is 500 \times 250 pixels. The optical beam is incident on the specimen from the top (intimal surface) and each vertical line in the image represents an axial measurement (500 pixels) of tissue reflectance. The image was formed by superimposing successive vertical scans (250) at different transverse positions. The false-colour scale is a log representation of backscattering intensity.

occlusion, but cannot differentiate vessel morphology. Other techniques such as intravascular ultrasound can provide an indication of morphology, but often lack the image resolution needed to identify high-risk plaque morphologies.

Optical coherence tomography is a promising imaging technology for intravascular imaging because it provides high resolution and can permit the imaging of high-risk plaque morphologies. An example of an OCT image of plaque in a human aorta *in vitro* shown in Fig. 2. The intimal surface of the aorta is clearly demarcated at the top of the image. The arterial wall is visualized in orange-yellow, indicating relatively high optical backscattering, whereas an intramural lipid deposit is differentiated as a dark area of low optical scattering (arrow). The OCT image clearly differentiates structural morphology, which would be difficult or impossible to detect by intravascular ultrasound. These preliminary results suggest that OCT is a promising imaging technology for the assessment of coronary artery disease.

In a more general context, OCT has the potential to provide morphological information in a wide variety of tissues for a range of clinical diagnostic applications. An example of an OCT image of human trachea is shown in Fig. 3. The lumen is oriented toward the top of the image. Structural details in the muscular and inner fibrous layers are visible as well as a secretory gland (labelled G) with a duct leading through the mucosa (labelled by arrows).

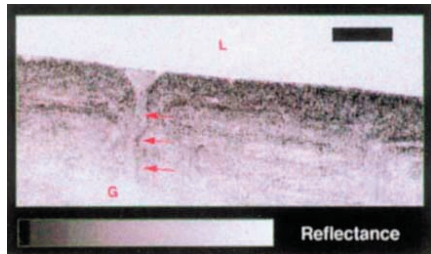


Fig. 3 An OCT image of human trachea *in vitro*. Glandular structures including the duct (arrows) leading to the lumen (L) are well differentiated in the image. The epithelial cell layer is evident as a thin boundary of reduced optical scattering on the intimal surface of the trachea. G, gland. Bar, 500 μ m. Other internal structures can be differentiated. The image was acquired using a 1,300-nm light source and is 500 \times 250 pixels. The grey scale is a log representation of backscattering intensity.

Images of this type demonstrate the ability of OCT to perform non-excisional measurements of morphological structure.

Summary

Optical coherence tomography is a new imaging technique that can perform high-resolution, micrometre-scale, cross-sectional imaging in biological systems. The technology has been developed, and reduced to, preliminary clinical practice in ophthalmology. The challenging problem that OCT may address is the development of 'optical biopsy' techniques. These techniques can provide diagnostic imaging of tissue morphology without the need for excision of specimens. Many investigations remain to identify optimal areas for clinical application, and additional engineering must be

done to integrate vertically the technology and to reduce it to clinical practice. Nevertheless, preliminary studies indicate the feasibility of developing this technology for a wide range of clinical and research diagnostic imaging applications. The ability to non-excisionally evaluate tissue morphology using a catheter or an endoscope could have a significant impact on the diagnosis and management of a wide range of diseases.

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