OPTICAL COHERENCE TOMOGRAPHY
PRINCIPLES, INSTRUMENTATION, AND BIOLOGICAL APPLICATONS

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1. Introduction

Optical coherence tomography (OCT) uses low coherence interferometric techniques to obtain high resolution (1 - 10 μm), high sensitivity (more than 100 dB) reflectivity profiles of a sample. One, two, and three dimensional images of the internal microstructure of a sample's optical properties such as refractive index, absorption coefficient, scattering coefficient, and birefringence can be obtained. The basic principles and limitations of OCT will be reviewed. The relative merits of OCT compared to other optical imaging modalities will be addressed. We have developed a system that provides "real time" 2-dimensional false-color tomographs. This unit has been used to diagnosis and treat over 2000 patents in an ophthalmic clinic. In this Chapter we will describe the design and performance of various OCT system implementations and present measurements on a variety of biological tissues.

Over the past decade there have been tremendous advances in biomedical imaging technology. For example, magnetic resonance imaging, X-ray computed tomography, ultrasound, and confocal microscopy are all in widespread research and clinical use and have resulted in fundamental and dramatic improvements in health care. However, there are many situations where existing biomedical diagnostics are not adequate. This is particularly true where high resolution (~ 1 μm) imaging is required. Resolution at this level often requires biopsy and histopathologic examination. While such examinations are among the most powerful medical diagnostic techniques, they are invasive and can be time consuming and costly. Furthermore, in many

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situations conventional excisional biopsy is not possible. Coronary artery disease, a leading cause of morbidity and mortality, is one important example of a disease where conventional diagnostic excisional biopsy can not be performed. There are many other examples where biopsy can not be performed or conventional imagining techniques lack the sensitivity and resolution for definitive diagnosis.

Optical Coherence Tomography (OCT) is a new imaging technology based on the coherence properties of light [1]. OCT has high-resolution, high-sensitivity and operates analogous to optical or RF radar. This technology has already made revolutionary impacts in the area of ophthalmology. MIT has designed, developed, and fielded a clinical instrument that is now operating at the New England Eye Center at Tufts University School of Medicine where it has been used to monitor and treat over 2000 patients. This particular OCT system attaches to standard existing ophthalmic instrumentation, is computer controlled, and produces high resolution real-time digitally processed images to clinicians. Early results indicate that this will be a major technological improvement in the diagnosis and treatment of ophthalmic diseases. We believe that this ophthalmic application is only the "tip of the iceberg" and that OCT is an information-age technology that will achieve micron-scale 2- and 3-D images for a wide range of new and important biomedical applications. Several research groups around the world are now working on further developing OCT. In the future we expect OCT to achieve a new level of visualization and diagnostic capability comparable to *in vivo histopathology* for a variety of biomedical appliations including: skin, bone, endoscopic, laproscopic, vasuclar, developmental biology, and dental applications.

2. OCT Technology Review

OCT uses optical coherence domain reflectometry (OCDR) to measure, along a single axis, optical properties of a sample (index of refraction, scattering coefficient, absorption coefficient, birefringence, etc.) using interferometric techniques and a short coherence length light source [2-4]. Figure 1 shows the basic concept. A broad bandwidth light source is coupled into a Michelson interferometer. One arm of the interferometer leads to the sample of interest, the other leads to a reference mirror. Reflected beams from the two arms are recombined in the beam splitter and detected on a photodetector. Due to the broad bandwidth properties of the light, only when the signal arm and reference arm optical path lengths are matched to within the source coherence length is interference detected. By mechanically scanning the reference arm path length, a reflectivity profile of the sample's microstructural detail is obtained. In contrast to many other optical ranging techniques, the Fourier transform-limited spatial resolution, determined by the spectral bandwidth of the source, can be achieved. The wider the bandwidth, the higher the resolution.

In order to make measurements of weakly reflecting tissue microstructure at high rates, high system sensitivity is required. The ultimate system sensitivity is determined by quantum mechanical noise effects [4]. In contrast to many other optical ranging techniques, which can be hundreds of times above their fundamental sensitivity, properly engineered OCDRs can be made to work at the quantum limite. We have demonstrated high speed quantum-limited OCDR systems with extremely large dynamic range ($>10^{12}$) using careful system design and compact, low-cost electronics and fiber optics. In the fields of fiber optics and optoelectronics, OCDR technology has already demonstrated unparalleled ability to resolve reflection sites, waveguide loss, dispersion, and birefringence within fiber optic, integrated optic, and active and passive semiconductor waveguides [2][5-7].

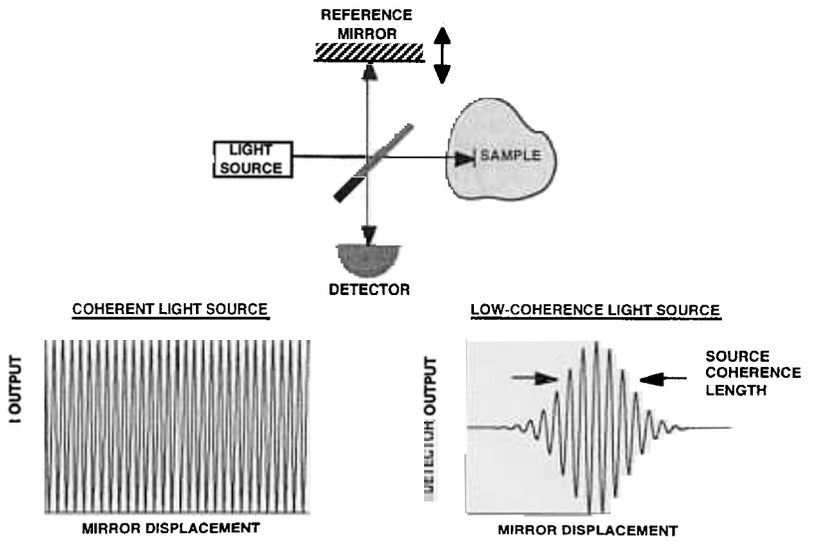

Fig. OCDR concept.

Optical coherence tomography (OCT) is an extension of OCDR technology to imaging in two or three dimensions [1][8]. Combining adjacent longitudinal scans and lateral scanning and then mapping the result into a false-color or gray scale image is one simple example of 2-D OCT imaging. Direct parallel acquisition in two and three dimensions is also possible. As in OCDR, the longitudinal resolution of OCT is determined mainly by the spectral properties of the source and the longitudinal point-spread function of the imaging optics. The lateral resolution is determined by the focusing optics, as in conventional optical microscopes. Figure 2 shows a schematic of one of our implementations of an OCT system.

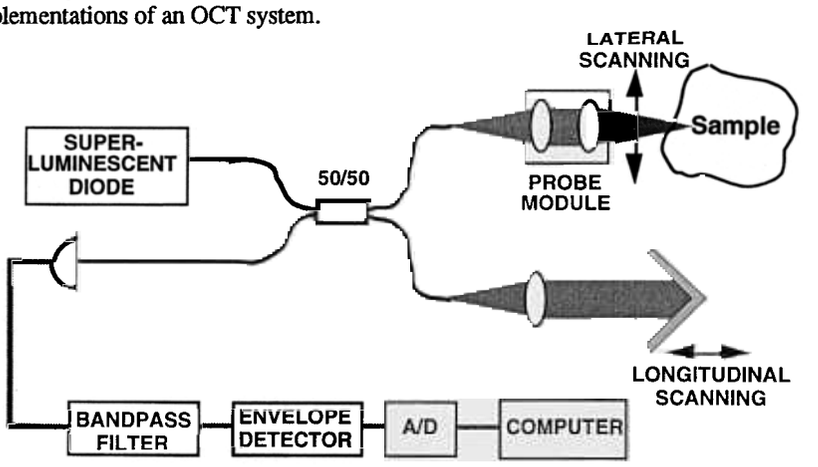

Fig. 2. OCT block diagram

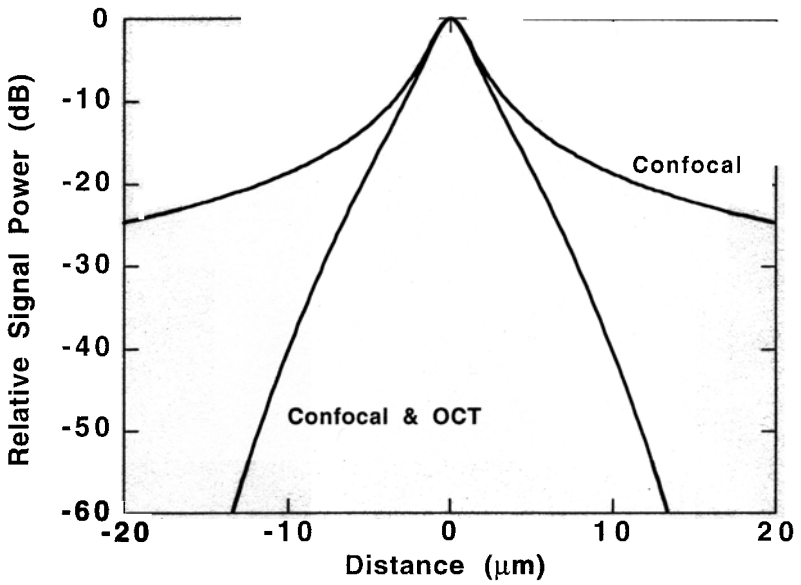

Fig. 3. Theoretical longitudinal point-spread functions.

In this example, a near-infrared fiber coupled super-luminescent diode (0.83 μm) is used as a source. A probe module couples light to and from the sample and performs lateral scanning either using fast galvanometric beam steerers or stepping motor stages. Longitudinal scanning is performed using a fast linear actuator. The system was designed at MIT for ophthalmic imaging and is under complete computer control and produces real-time false-color images.

Confocal microscopes offer one of the best existing solutions to imaging within highly scattering media. OCT is a confocal microscope by virtue of the fact that it utilizes interferometry. However, in many applications it offers a much higher longitudinal resolution and orders of magnitude better longitudinal point spread function contrast than existing confocal microscopes. This is a key technical advantage that can be exploited to allow high resolution imaging inside highly scattering media like biological tissues. Figure 3 shows the theoretical longitudinal point-spread function of a microscope and a confocal OCT microscope. Note that for this example, a normal microscope focused at zero would receive about -25 dB of cross-talk (or out-of-plane scatter) from reflections located ± 20 μm above and below the focus. An OCT based system could reduce that cross-talk by more than 1000 times (less than - 60 dB). This key OCT advantage facilitates the ability to image inside highly scattering media [9][10].

Figure 4 shows a measured longitudinal point-spread function demonstrating this improved discrimination. The source used in this example has a wavelength of 1.3 μm and a coherence length of ~ 15 μm. The full-width-half-maximum of the longitudial point spread function of the optics is 125 μm. Note that when confocal imaging alone is used (curve labeled focus only) the point spread function decays as $(\text{displacement})^{-4}$. When coherence gating alone is used the point spread function decays according to the Fourier Transform of the source spectrum - that is, according to its autocorrelation function. For a Gaussian spectrum, the point spread function is also a Gaussian function. The SLD used in this experiment had an approximately Gaussian spectrum and as seen in Figure 4 has a much sharper longidudinal point spread function. However, most optical sources do not have precise Gaussian spectra, particularly in the "tails of

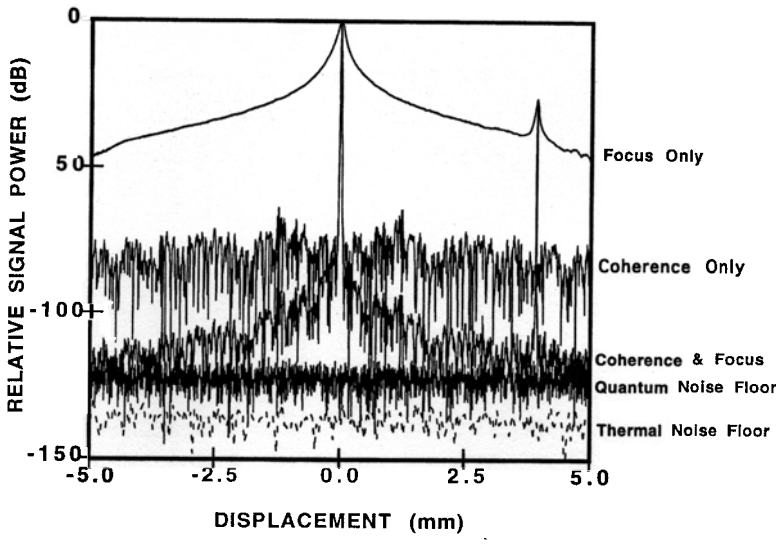

Fig. 4. Measured longitudinal point-spread functions.

the spectrum". Nonidealities in the spectra lead to blindness limitations [5][11]. As shown in Figure 4, for this particular SLD, the blindness limitation created a floor in the dynamic range at about -80 dB. Thus for this particular source, a stong reflection within a biological sample will mask all other waker reflections of relative magnitude -80 dB or lower over a range of ± 5 mm from the strong reflection site. By combining focusing with coherence gating one achieves the product of the two point spread functions thereby extending the dynamic range. As seen in Figure 4 a dynamic range of over 125 dB can easily be achieved. Note the spike at approximately +4.0 mm is due to an artifact in the focusing lens. Thus it is not only the bandwidth but the details in the shape in the spectrum that are important for OCT.

There are many important features of OCT technology that are poised to make dramatic contributions to the field of biomedical imaging. These include the system simplicity, high longitudinal resolution, high sensitivity, and high contrast longitudinal point spread function.

3. Instrumentation

OCT instrumentation can be broken down into a few major subsystems. These include the: 1) Optical Source; 2) Interferometer; 3) Delivery Optics; 4) Scanning; 4) Detection, and, 5) Control. In this section we briefly will discuss some of the basic considerations associated with these aspects of the OCT instrumentation.

3.1. OPTICAL SOURCE

The characteristics of the optical source are important factors in an OCT system performance. Four of characteristics of interest are wavelength, power, coherence length, and autocorrelation function. The commercial telecommunications and optical storage industries have developed sources that are readily available at 0.63, 0.78, 0.83, 1.0, 1.3, and 1.55 μm. The choice of wavelength is strongly dependent on the indteded application. The longer wavelength tend to

penetrate deeper into many biological media and are therefore preferable. Sources we have worked with include, semiconductor sources (light emitting diodes (LED), edge emitting diodes (ELED), superluminscent diodes (SLD)), mode-lock lasers (e.g. Ti:Al_2O_3, Cr:Mg_2SiO_4, Cr:$LiSrAlF_6$), rare earth doped fibers (Yb, Nd, Er, Pr, Tm), and super-continuum sources. LED and ELED devices are very-low cost broad bandwidth devices having coherence lengths less than 10 μm. Their main limitation is that typically they have very low power (< 100 μW) when coupled into a single spatial mode. The design of SLDs has rapidly progressed over the past several years. Efficient multi-quantum well devices with very low spectral ripple are commercially available. Presently commercial SLD's offer the best choice for cost, portability, short coherence length (~ 10 μm), and power (~ 2 mW). Actively and passively mode-locked lasers offer very high power (> 100 mW) and short coherence length (< 5 μm) [12][13]. However, in most cases they are not very portable require dual balanced receivers to cancel excess intensity noise and are typically used in laboratory settings. Rare earth doped fibers are a very promising candidate for future OCT systems. They are robust, portable, and potentially low cost. Key to the success of these devices is the insertion of Bragg gratings within the gain medium to prevent the ASE spectra from narrowing at high power. In the near future source powers in excess of 100 mW and coherence lengths under 10 μm will be demonstrated. Super-continuum sources use high peak powers and external nonlinear media (such as self phase modulation in silica fiber) to generate very broad spectra [14][15]. For instance at 1.55 μm it is quite easy to generate powers in excess of 1 W with coherence lengths less than 10 μm using gain switched lasers, high power Erbium amplifiers, and dispersion shifted fibers. However, these sources typically have poor spectral characteristics resulting in severe blindness limitations.

3.2. INTERFEROMETER

There are several varieties of interferometers used in OCT systems (Figure 5). The most widely used is a simple Michelson Interferometer as depicted in Figure 1, 2. Its attractive features include simple fiber and bulk optic implementations and efficient use of signal power. Figure 5a, shows a modified version of this employing a dual balanced excess intensity noise canceling receiver. As mentioned above this is important for lasers with significant intensity noise such as mode-lock lasers. One limitation in studying living biological samples is that motion of the sample during the measurement will show up as distortions in the image. Faster scanning helps eliminate motion induced artifacts. However, in most living biological tissues there is a limit to how fast scanning can be accomplished due to the finite signal power that can safely be delivered to the specimen. Signal processing techniques can help eliminate any residual motion induced artifacts [8]. However, other interferometric embodiments have been developed to help elevate motion induced artifacts or artifacts related to fluctuations within the delivery system itself (e.g. fiber heating). Figure 5b and 5d shows two additional simple configurations. By placing a reference reflection near or on the sample, a differential measurement between the reference reflection and sample is possible. Thus the measurement is insensitive to any path length variations along the sample arm. In fact the distance to the sample can be made very large. One of the drawbacks of these approaches is they are less efficient in the use of signal power reflected from the sample (> 3 dB loss) and more over, in some cases the reference signal power is not sufficient to maintain shot-noise-limited operation thereby sacrificing overall system sensitivity.

For most OCT systems, particularly those involving fiber optic delivery systems, polarization sensitivity can be a concern. Interferometric detection requires alignment of the reference and signal polarization vectors. If the delivery fiber is moved or heated, or if the biomedical sample of interest is birefringent, then signal fading can occur. Polarization preserving fibers are not very effective in eliminating this proplem due to their inability to precisely maintain

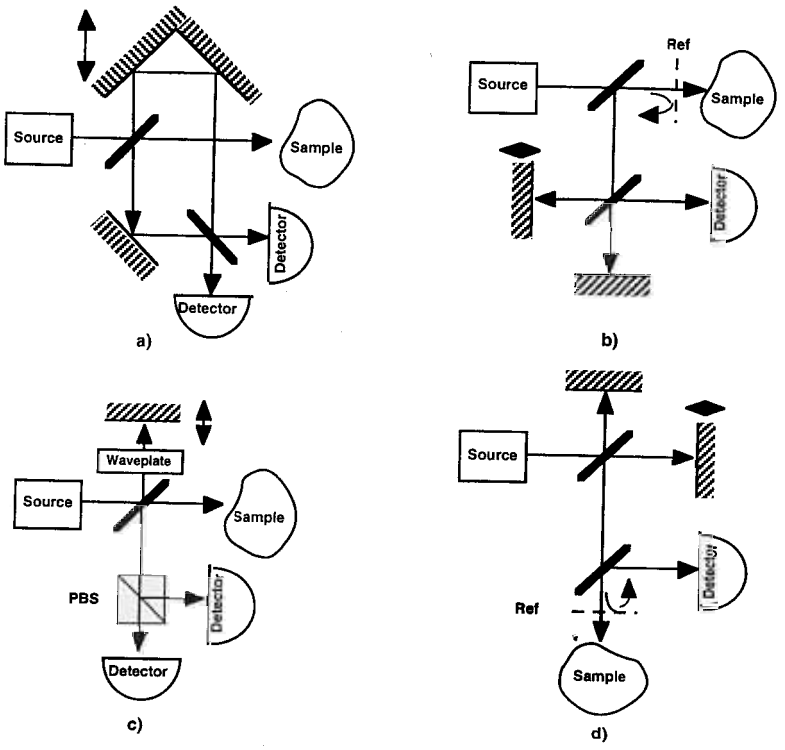

Fig. 5. Example OCT interferometer types.

polarization. The most successful approaches have involved using polarization diversity receivers as shown in Figure 5c [6][16]. The added benefit of this approach is that micron scale birefringence measurement of the sample can be obtained.

3.3. DELIVERY OPTICS

For scanning embodiments, single-mode fibers are an attractive method for coupling light to and from the sample. This is due to the low cost of fiber components and the modularity and flexibility that fibers provide. As shown in Figure 2, a bulk optic probe module is still required to couple light to and from the sample. One of the principle design features of this probe module is the inherent tradeoff between longitudinal scanning range (depth-of-field) and lateral resolution - as is the case with conventional microscopes. The lateral resolution is proportional to 1/F# and the depth of field is proportional to $(1/F\#)^2$. Thus achieving high lateral resolution comes at the expense of scanning depth. For a Gaussian beam the FWHM confocal distance is $Z_{cf}=2\pi\omega_o^2/\lambda$, where ω_o is the e^{-2} beam waist radius, and λ is the source wavelength. For a 20 μm lateral resolution the depth of field is ~ 800 μm at a wavelength of 0.8 μm. With the large dynamic range of OCT one can scan significantly beyond the confocal distance. However, for very high lateral resolution (1 μm) the scanning depth is limited.

Several methods exist to overcome this limitation. One approach is to scan the focusing lens in synchronism with the reference mirror. However, this is problematic in that the relative motion is proportional to the sample index of refraction which may not be constant. Another limitation of

this approach is that it is difficult, from a mechanical viewpoint, to rapidly slew the focusing lens. At low rates we have successfully implemented this approach. An alternative which addresses the mechanical consideration is to perform lateral instead of longitudinal priority scanning. In this case the focusing lens can be moved much more slowly. However, as discussed in the next section complications arise from the need to frequency shift the reference light.

3.4. SCANNING

Two types of scanning are required for serial acquisition systems - lateral and longitudinal scanning. The priority of the scanning can be interlaced longitudinal scans (longitudinal priority) or interlaced lateral scanning (lateral priority scanning). Lateral scanning is typically performed with galvanometric, polygonal, or stepper motor stages. Several different options exist for longitudinal scanning as shown in Figure 6. One of the simplest approaches for longitudinal scanning is to use stepper motors. They are precise, readily available, and well suited for high sensitivity lock-in detection techniques. Their main limitation is that they are very slow, costly, and do not have a uniform velocity profile. Many high speed longitudinal priority applications require a near uniform velocity. This makes detection and registration of the information easier.

We have investigated several techniques for high speed near uniform velocity profiles. As shown in Figure 6, small retro-reflectors attached to galvanometric beam steerer offer the most straight forward approach and are suitable to repetition rates of ~ 100 Hz and strokes of ~ 5 mm. PZT ceramics, used to stretch wound coils of fiber, may achieve higher speeds (~ 1 kHz) and strokes of ~ 5 mm. To prevent polarization scrambling a Faraday mirror is used to reflect the output light. Faraday mirrors have the property of unscrambling the polarization upon return of the light at the input. The present limitations of this approach include linearity and hystersis problems associated with the PZT, the need for a very high voltage drive, and imperfections in the Faraday mirror. Spinning helical mirrors and helical cams offer an attractive approach for uniform very high velocity scanning. They are limited to strokes of ~ 5 mm and are difficult and costly to fabricate. An approach offering very large stroke (>10 mm) but low repetition rates involves a retro-reflector attached to a lead screw.

3.5. DETECTION

The key to the detection and demodulation subsystem is to achieve high sensitivity and high dynamic range. The ultimate sensitivity is dictated by quantum mechanical effects. The minimum resolvable reflection is given [4] by $R_{min} \sim 3.5(v/\Delta L)/(\eta P_s/h\nu)$, where v is the longitudinal velocity, DL is the source coherence length, η is the detector quantum efficiency, P_s is the incident source signal power, h is Planks constant, and ν is the optical frequency. This expression can be interpreted as needing to receive at least one photon per coherence cell in the sample. Thus if the sample is rapidly scanned (in terms of the number of coherence-cells/seconds) then a large signal power is needed. One important design rule is to achieve this ultimate sensitivity is perform heterodyne detection. This moves the interferometric signal away from baseband and any associated 1/f-type noise and line pickup. For high speed uniform velocity longitudinal priority scanning one can rely on the Doppler frequency shift associated with the moving reference mirror to frequency shift the light as shown in Figure 2. The electronics in this case simply involve bandpass filtering and either envelope detection or detection via logarithmic amplifiers. In this modality the i.f. filter is set to ~ 2 times the coherence length pulse width. Narrower filters (e.g. matched filters) yield slightly increased sensitivity but sacrifice resolution by temporally smearing out the impulse response. Wider filters let in unnecessary noise.

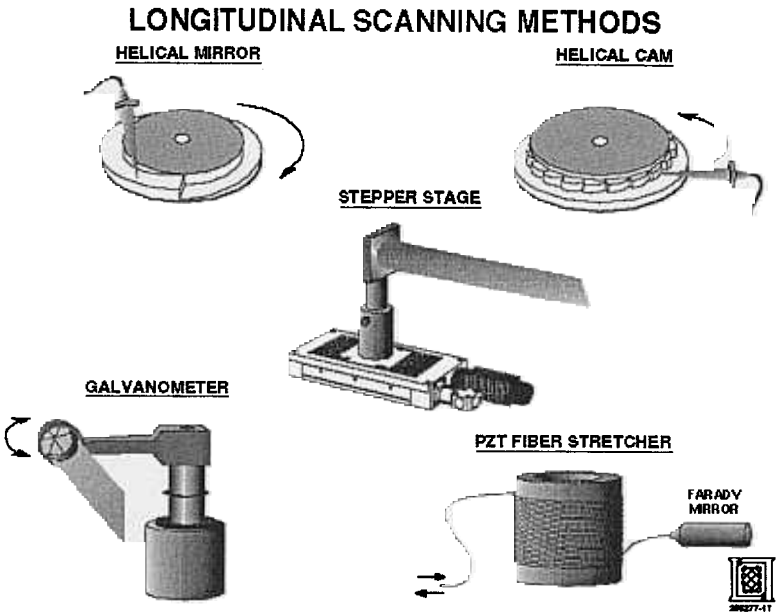

Fig. 6. Example longitudinal scanning mechanisms.

One of the simplest techniques for low-rate scanning that achieves high sensitivity is to use stepper motor stages and lock-in amplifier techniques. In this case the i.f. frequency shift may be accomplished by stretching the reference arm fiber in fiber optic implementations or dithering the reference mirror in bulk optic implementations. A saw-tooth waveform with an round-trip amplitude of 1 wavelength effectively implements a serrodyne frequency shift. This technique for frequency shifting can also be used for lateral priority scanning. An alternative method for frequency shifting is to use acousto-optic modulators. However, they typically implement a higher frequency shift than desired, have throughput loss, and can cause dispersion. For very high image acquisition rates (e.g. video rates) combined with transverse priority scanning AO offers an effective solution.

Most OCT systems utilize envelope detection. For widely space reflection sites one can easily resolve distances to much less than the coherence length limited resolution by using simple centroiding techniques. However, in turbid tissue or with very closely spaced reflection sites resolution is limited to approximately the coherence length with envelope detection. It is widely known that utilizing the phase information can in many situations provide enhanced resolution. Several groups are developing phase sensitive detection techniques and inverse scattering theory to extract enhanced resolution. In the near future OCT systems based on fast digital signal processing technology will be demonstrated enabling the ability to do phase sensitive detection, velocimetry, and spectroscopic measurements.

4. Biomedical Applications

There are a wide range of biomedical applications for OCT. Examples include ophthalmology, microscopy, endoscopy, laproscopy, determotology, developmental biology, densitry, etc. [17-24]. This section will briefly describe a few of these biomedical application areas.

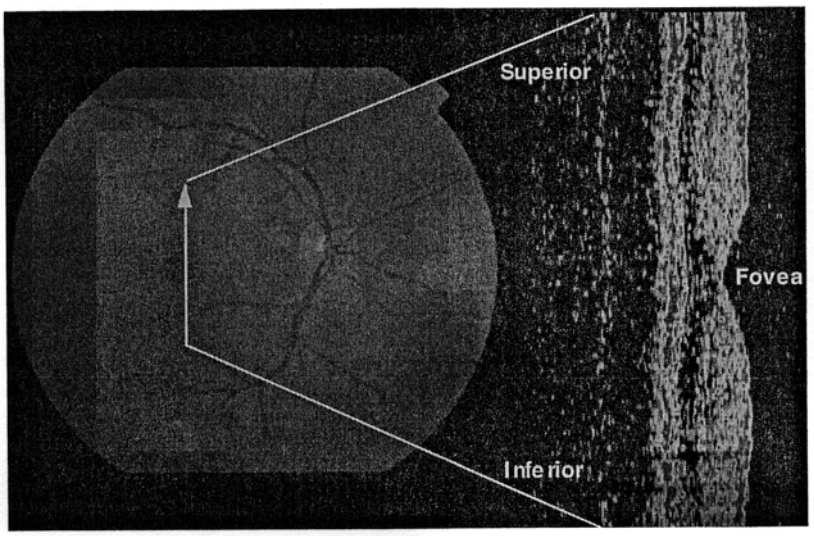

Fig. 7. In vivo optical coherence tomogram of human retina.

At MIT our initial focus was in the area of ophthalmology. We have developed an ophthalmic OCT instrument that is now in clinical trials at the New England Eye Center at Tufts University Medical School. Over 2000 patients have been examined with the OCT instrument. Figure 7 contains an fundus photograph of a human retina and a typical OCT false color image obtained with the prototype unit. The resolution of this tomography is approximately 10 to 100 times better than any other existing technology. Early results from the clinical trials indicate that OCT will offer a major improvement over more conventional technology in the diagnosis and treatment of ophthalmic diseases [8][17-21].

Microscopy is another important application area. As stated above, OCT is a confocal microscope but has the added benefits of coherence gating. In the ophthalmic application the lateral resolution is limited by the F# of the eye. In microscopy applications much higher lateral resolution is available - to the point where cellular level image is possible. To demonstrate feasibility we have examined an onion skin. Figure 8 contains a 3-D image. Shown are six different 2-D cellular level images spaced 100 μm apart in depth. High contrast is obtained at each plane in spite of the extremely weak reflections from the cells and the large amount of scatter that exists throughout the medium.

One of the promising future opportunities for OCT is its abilitity to perform optical biopsy within highly scattering tissue [22]. One of the current focuses of the OCT work at MIT and MGH is in intravascular imaging. Acute myocardial infarction (AMI) is the leading cause of death in the industrialized world. Presently the ability to predict sites in the coronary artery likely to lead to AMI is poor, primarily because of the low resolution produced with currently available imaging technologies such as angiography, ultrasound, and MRI.

We have performed *in vitro* studies which demonstrate that OCT yields sufficient resolution to identify structural features of atherosclerotic plaques [1][22-24]. Figure 9 shows an OCT image of an inferior mesenteric artery branch. demonstrating imaging can be performed through the entire vessel thickness. OCT shows considerable promise as a diagnostic technology for acute coronary syndromes. Because OCT uses single mode fiber optics, it can be integrated into intravascular catheters in a manner similar to intraluminal ultrasound or other catheter based diagnostics.

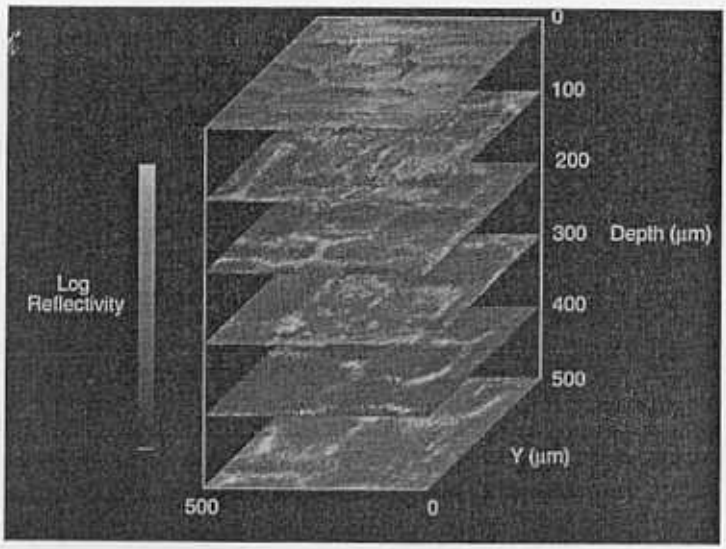

Fig. 8. OCT 3-D cellular imaging capability.

5. Conclusion

This Chapter has reviewed some of the principles of OCT, issues related to instrumentation, and presented some biomedical imaging applications. OCT has already demonstrated dramatic contributions to several areas of biomedical imaging. In order for this technology to grow several technological achievements will be required. These include improvements in optical sources, longitudinal scanning mechanisms, delivery and imaging optics (e.g. catheters), and high speed

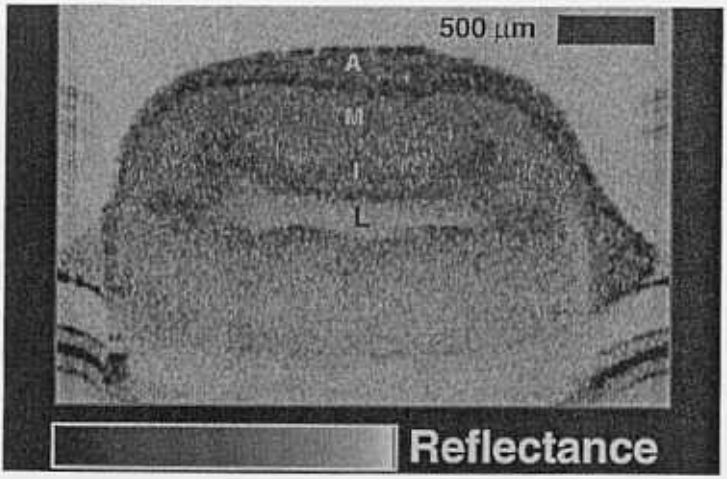

Fig. 9. OCT image (*in vitro*) of an inferior mesenteric artery branch. The adventita(A), media(M), intima(I), and lumen(L) are clearly demarcated.

detection and demodulation techniques. As the instrumentation technology develops we will explore new applications and enhance the effectiveness in existing ones. We expect the technology to evolve into clinical trials in new areas such as cardiology and endoscopy. OCT is one of the few technologies promising micron scale resolution in highly scattering media - comparable to *in vivo* histopathology. The future for OCT seems very bright.

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