Latest Trends in Optical Coherence Tomography (OCT)

By John Black

Executive Summary

Optical Coherence Tomography (OCT) is an imaging technology using non-ionizing radiation that can analyze tissue structure to a depth of 1 to 2 mm with routine depth resolution of 2 to 20 microns. It can be used to detect disease conditions that modify tissue organizational structure, such as early carcinogenesis, atherosclerosis, glaucoma, tooth cavities, and potentially the effects of Alzheimer’s on the optic nerve. It can potentially be used to support any medical procedure that benefits from real-time tissue structure information, such as highly accurate placement of a drug or device, or to assess treatment effects that change tissue structure such as cauterization or ablation.

OCT falls between ultrasound and confocal or traditional microscopy in terms of penetration depth and resolution but gives intuitively interpretable images, for example the cross-section of a healthy coronary artery below where the single-cell layer intima/internal elastic lamina, media (smooth muscle cells) and adventitia (the strength member of the artery wall) can all be clearly differentiated.

Image Source: Triermain, LLC.

In the future, we’ll see OCT applied to

- Real-time precision guidance of injections where the therapeutic must be injected directly into the target tissue (chemotherapy for example),
- Precision placement of stem cells which must be placed in the tissue that they are intended to treat so that they can be “programmed” by the molecular environment around them,
- Precision placement of electrodes for neuro-modulation, for example in the treatment of tremors or chronic pain, where OCT can not only identify the nerve bundle embedded in the tissue but also can identify the specific part of the nerve bundle or perhaps even an individual nerve requiring stimulation or ablation.
• Real-time guidance in surgical robotics, particularly ophthalmology, where the precision of OCT can guide the robot exactly to the target with sub-50-micron precision thereby avoiding collateral damage.

Practically speaking OCT will also benefit from leveraging recent developments and methodologies in compact LIDAR for autonomous vehicles, including the optical assembly and test techniques being developed to bring the high levels of reliability required for consumer products to complex optical instrumentation. A new class of compact, all-fiber/all-solid-state swept sources with linear frequency tuning and integral fine-grained triggering clocks currently under development will obviate the need for $k$-space renormalization and thereby speed up the ability of the imaging hardware to process and display the OCT data in real time.
What is OCT?

OCT (Optical Coherence Tomography) is the optical analog of ultrasound, allowing depth-resolved imaging in biological tissue or scattering media. Where ultrasound has around ~100-micron (µm) resolution over several centimeters of penetration depth, OCT has sub-10-µm resolution over 1 – 2 mm of penetration. OCT can be thought of conceptually as a time-of-flight experiment (like pulsed Laser Detection and Ranging (LADAR)). A device launches light into the target tissue, and the detector identifies photons that have reflected from interfaces in the tissue via time-of-flight experiment, where the speed of light in tissue and the round-trip time for the photon tells you how far it travelled. In the case of OCT in tissue, unlike LADAR, the actual distance travelled is of the order of a few mm, so the round-trip time-of-flight is on the order of 10 picoseconds. This is too short a round-trip time to measure accurately with reasonable equipment in the time domain, so the measurement is transformed into either the length or frequency domains.

OCT was originally implemented in a classical Michaelson-Morley interferometry experiment (so-called Time Domain (TD) OCT) analogous to the Laser Interferometer Gravitational-Wave Observatory (LIGO), where the interference signal (interferometer “fringes”) generated by coherently combining the signal from the sample arm containing the tissue and a reference arm is measured as a function of the position of the reference arm mirror. The need to move the reference mirror accurately and repeatably on the micron-scale imposes speed constraints on the measurement time, which in turn practically limits the time to sample the depth-resolved signal at a particular beam position to around 200 – 250 microseconds (µs), restricting sampling to 4 – 5 kHz (the OCT A-line rate).

Swept-source (SS) OCT is one of two contemporary Fourier-Domain (FD) techniques in OCT that offers very significant improvements in signal acquisition rates and signal-to-noise ratios over the more traditional TD-OCT. In SS-OCT, the time-resolved remittance of a sample under illumination from a chirped (rapidly wavelength swept) source laser is coherently combined with a chirped local oscillator (the reference signal) and thereby amplified by the process of Coherent Detection1 as a result of which we can potentially detect one photon per second with 1 sigma confidence in a bandwidth of 1 Hz, i.e. with great dynamic range and sensitivity. This signal is then digitized and processed mathematically, ending with a fast Fourier Transform (FFT) which has the effect of transforming the data from amplitude vs. frequency space to intensity vs. length (depth). The chirp rates of the lasers used in SS-OCT are set up so that the beat notes (difference frequencies) resulting from heterodyne detection step appear in the DC-100 MHz range (for example). In this manner we can make a time-of-flight measurement of picoseconds with femtosecond resolution in the RF frequency domain, which is significantly more convenient / cost-effective / faster / easier than trying to move a delay line mirror with the requisite speed and precision. FD-OCT is an adaption of a technique from chirped-pulse RADAR – it turns out that the RF and microwave folks have had coherent radiation going back to the 1930’s, far longer than the optics nerds!

SS-OCT and Spectral Domain (SD) OCT (the second variant of FD-OCT) offer the chance to improve sampling rates by up to three orders of magnitude over TD-OCT. FD-OCT preserves the Fellgett Advantage; the √N improvement in SNR for N measurements discovered by Peter Fellgett in 1949, the same year Claude Shannon developed Information Theory. It also preserves the Jacquinot Advantage of lossless imaging as, with the right interferometer configuration, brightness is conserved from source to detector (no slits or dispersive elements to shed signal).

OCT is implemented in 3 main wavelength ranges, defined by their center wavelength. The depth of penetration in tissue is proportional to the center wavelength – the shorter the wavelength, the

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shallower the depth of penetration. The resolution of OCT is proportional to the emission bandwidth of the laser (over what wavelength range the source emits light) divided by the square of the center wavelength.

The wider the optical bandwidth of the laser, the sharper the resolution; the shorter the center wavelength, the sharper the resolution. For an axial resolution requirement of 10 microns, we may determine the system bandwidth of the OCT system using:

\[ \partial z = \frac{2 \ln 2 \ \lambda_0^2}{\pi n \Delta \lambda} \]

Assuming \( n = 1.4 \) (a reasonable upper limit) and a center wavelength of 1310 nm we are led to a minimum laser bandwidth of 54 nm for 10-micron-axial resolution. Modern laser sources routinely have bandwidths of 100 nm and more, comfortably achieving the resolution specifications while offsetting the effects of clipping and vignetting in the components.

The intensity of the returned scattered light is also a sensitive function of the probe wavelength, varying as \( \lambda^3 \) to \( \lambda^4 \) over contemporary OCT wavelength ranges. Ophthalmology is usually performed at 800 – 850 nm center wavelength, with some work done at 1050 nm. This takes advantage of the increased resolution and increased intensity of the back-scatter at this center wavelength while recognizing that in retinal imaging, the penetration depth, which is reduced at 800 nm, is a secondary issue given that the really important data from a retinal image are present in the first 500 – 750 microns of tissue. Ophthalmology is, by far, the medical discipline where OCT has had the most substantial impact to date, and, working on the paradigm that the eye is a window on the brain, is likely to be so for the near future.

OCT gives intuitively interpretable images requiring minimal learned-pattern-recognition, for example the cross-section of healthy coronary artery below compared to a text-book histology cartoon, where the single-cell-layer intima/internal elastic lamina (the endothelium), media (smooth muscle cells) and adventitia (the strength member of the artery wall) can all be clearly differentiated.
The other medical discipline where OCT has found a niche is in cardiovascular imaging and therapeutic guidance, where coronary artery disease (atherosclerosis) can now be imaged from its molecular/structural beginnings to being symptomatic to being treated. 

[https://californiaconsultants.org/wp-content/uploads/2018/09/CNSV-1810-Black.pdf](https://californiaconsultants.org/wp-content/uploads/2018/09/CNSV-1810-Black.pdf) Cardiovascular OCT imaging is almost always done at 1310 nm center wavelength (the telecom O-band) where the massive advances in fiber-optics, laser sources and detectors that have powered the telecom revolution of the last 20 years have been elegantly applied in medical devices.

- **What are the alternatives?**

  OCT falls between ultrasound and confocal or traditional microscopy in terms of penetration depth and resolution as shown by the following slide (Image credit Jennifer Barton – University of Arizona)

  ![Depth of Penetration](Image)

  In the biophotonics community imaging modalities are often sub-categorized into structural and functional imaging techniques. Structural imaging shows the way the cells and tissues are arranged in space, how they interconnect etc. Abnormal cell clusters or growth can sometimes be differentiated from normal tissue by observing the organization of cells in and around the growth, however it can be hard to differentiate benign new growth from suspicious without additional information. Functional imaging is primarily concerned with molecular information, such as that obtained in traditional microscopy when tissues are sectioned and stained with various fluorophores to elucidate the presence of specific molecules and whether these molecules are being up- or down-regulated, for example indicating the presence of carcinogenesis.
OCT, like ultrasound, is primarily a structural imaging technique, showing cell layers, mesoscopic organization, and the interfaces between different types of tissue based on refractive index changes. Refractive index can be thought of as a measure of the speed of light in tissue – the larger the refractive index, the more light slows down in that medium. OCT is very sensitive to step functions and steep gradients in refractive index, and to the light scattering characteristics of the small (often sub-wavelength) organelles and structures within cells. As shown above in the picture of the coronary artery, the smooth muscle cells in the media are largely hypo-intense (weakly back-scattering) despite being well structurally organized and presenting a broadside of refractive index steps to the light. The adventitia on the other hand is hyper-intense despite being largely composed of collagen and elastin, molecular level organization nominally sub-wavelength in scale.

OCT can give some functional (molecular) information, however other techniques such as optical fluorescence, Raman spectroscopy, IR absorption spectroscopy and even MRI are superior for molecular content. A case where OCT can provide timely, clinically relevant molecular information is in the difference between lipid-rich and normal hydrated tissue, as shown below in the picture of a coronary artery wall harboring a thin-cap fibro-atheroma (TFCA), a so-called “vulnerable plaque” thought to be one of the root causes of sudden cardiac arrest through myocardial infarction.

The left-hand-side image shows the major, frequently-observed components of a heavily diseased artery wall with intimal hyperplasia 11 – 12 o’clock, calcium hydroxy-apatite deposits (“hardened arteries – a very real phenomenon) and thick atheroma at 4-o’clock. The interesting structure at 5 – 6 o’clock, with the bright thin tissue over a hypo-intense void is characteristic of a thin fibrous cap over a lipid-rich crypt. The brightness of the cap is caused partly by the large refractive index change from fibrous to lipid-rich tissue (analogous to a Fresnel reflection). Rupture of the thin cap causes the crypt material underneath to spill out into the vessel lumen. This material is intensely thrombogenic, immediately nucleating a blood clot with catastrophic consequences for oxygenation of the heart muscle – a “heart attack”.

- **What are particular advantages compared to alternatives?**

OCT has several advantages in terms of application to medicine in that it can be implemented in
surgical tools and bed-side system using minor modifications of contemporary telecommunications technology. It obviously has close-to-histological image resolution which allows the presentation of intuitive images to a clinical practitioner with minimal learned pattern recognition. It has excellent depth perception/resolution, allowing it to be incorporated into robotic surgery as a collision avoidance mechanism with minimal latency, allowing a tool to move precisely and quickly around the tissue. It has the extremely high intrinsic bandwidths characteristic of fiber optics (GB/sec), very high levels of immunity to EM/RF interference, and can have minimal physical/mechanical impact on a surgical tool, since the fibers themselves can be around 100 microns in diameter so do not contribute significantly to the crossing profile or weight of a surgical device. For example the picture below shows a 155-micron OD optical fiber (light brown color) on the outer diameter (blue) of a 6-Fr (2 mm diameter) catheter. As can be seen the presence of the fiber can be made to be insignificant while adding tremendous capability to the tool.

- What you do see as the latest trends?

I think in the near future the application of OCT technology in medicine will be driven primarily by:

a) The increased adoption of OCT as a modality for therapeutic guidance.

The first OCT-guided therapeutic procedure in humans was done in September 2006 as part of the Foxhollow Technologies Nighthawk™ program to enable image-guided arterial plaque excision (atherectomy). (http://www.medicalnewstoday.com/articles/51482.php). Since then real-time OCT guidance has been applied in other cardiovascular specialties, and to ophthalmology where the exquisite precision and resolution of OCT can be applied to the most delicate retinal surgeries.

In the future we'll see OCT applied to real-time precision guidance of injections where the therapeutic must be injected directly into the target tissue (chemotherapy for example), precision placement of stem cells where the cells must be placed in the tissue that they are
intended to treat so that they can be “programmed” by the molecular environment around them, and precision placement of electrodes for neuro-modulation, for example in the treatment of tremors or chronic pain, where not only can OCT identify the nerve bundle embedded in the tissue but also can identify the specific part of the nerve bundle or even an individual nerve requiring stimulation or ablation. Recent (unpublished) work has shown that OCT has the ability to monitor in real-time the action of neuralytic agents acting on nerves; this in turn will allow titration of therapeutics to impact the nerve while minimizing collateral damage to the peri-nerve tissue.

b) New generations of compact frequency-modulated (FMCW) laser sources (including on-chip designs) being created by developments in compact LIDAR for autonomous vehicles and other applications.

For the Fourier Transform to work to convert the data from the frequency to length dimensions, the heterodyne photodiode signal must be digitized at equally spaced optical frequency increments. Unfortunately contemporary lasers typically used in SS-OCT do not sweep linearly in frequency as a function of time; often they do not even sweep in a manner than can be described by a low-order polynomial. This means that the A-to-D converter output of a block of photodiode data digitized at equal time intervals cannot simply be scaled, windowed then sent to the FFT routine. The digitized signal must be resampled (interpolated) using a reference clock signal so that the resampled array is composed of linear-in-frequency digitized values. This resampling / interpolation process is known in the OCT community as \textit{k-space renormalization}. It is computationally intensive, and as such slows down the processing of the incoming data stream, requiring that dense data be either streamed to a RAID and post-processed, or compacted / compressed for real-time presentation to the clinical practitioner.

We have found previously that image quality (defined as a combination of contrast, resolution, brightness (dynamic range), lack of latency) is the \textit{sine-qua-non} in real-time OCT therapeutic guidance, so compaction is really not optimal. A new class of compact, all-fiber / all-solid-state, unidirectional, linear-in-\textit{k} swept sources with integral fine-grained \textit{k}-clocks under development will obviate the need for \textit{k-space renormalization} and thereby speed up the ability of the imaging hardware to process and display the OCT data at full resolution with minimal latency. This in turn will advance the adoption of OCT in real-time image guidance of therapeutics.
About the author:

Triermain, LLC., is a San Francisco Peninsula-based R&D / Technology consulting firm specializing in the development of lasers and novel fiber optics techniques, and applying these developments in biophotonics, image-guided surgery, life sciences and remote sensing.

Bio

John Black founded Triermain in 2011. He has over 20 years of experience in the medical, scientific/research and industrial segments of the photonics industry and currently consults in laser design and development, optical coherence tomography (OCT), medical device design and development, image-guided surgery and optical remote sensing. John has a B.Sc. in Chemistry with First Class Honors, and a Ph.D. in Physical Chemistry from the Univ. of Nottingham. His Ph.D. work with Professor Ivan Powis centered around the use of Resonance Enhanced Multi-Photon Ionization (REMPI) to study molecular spectroscopy and dynamics, yielding one of the earliest fully-rotationally-resolved spectra of an electronically-excited state of the crucial CH\textsubscript{3} radical, simultaneously one of the earliest fully-rotationally-resolved spectra of any polyatomic photofragment.

He received an SERC/NATO Research Fellowship to do post-doctoral research in photochemistry studying with Professor R.N. Zare at Stanford Univ., studying the photodissociation of cyanogen iodide using sub-Doppler spectroscopy, and confirming the remarkable observations of Hasselbrink et.al. finding chirality (“handedness”) in an essentially achiral proto-system. He was a post-doctoral research fellow at Columbia University, developing a new tunable single-mode laser for molecular spectroscopy and reaction dynamics. At Coherent Medical, he managed the R&D Laser/Tissue Engineering group, and spearheaded the development of flagship surgical, ophthalmic and dermatologic applications of lasers – pioneering a new treatment of cutaneous vascular lesions. He then joined Lightwave Electronics (which became JDSU, Inc., and is now Lumentum), working initially on advanced fiber lasers for RGB projection systems in consumer electronics, (and subsequently on the design of the Xcyte™ mode-locked ultraviolet laser for flow cytometry.

At FoxHollow Technologies, he led the optical engineering team in the successful development of Nighthawk™, the first-in-man intravascular image-guided plaque excision catheter. This was the first real-time optical coherence tomography (OCT)-guided intravascular surgical procedure performed in humans, and possibly the earliest OCT-guided human surgical procedures of any kind. After FoxHollow, he led the imaging team at Avinger in the development of OCT-guided catheters for the treatment of chronic total occlusions, a severe end-stage form of peripheral / coronary artery disease that can lead to amputations and bypass surgery. The Ocelot™ OCT-guided CTO crossing catheter is FDA-approved and on the market.

John has 11 issued patents and more pending applications in the fields of laser development, biophotonics, optical diagnostics and medical devices. He is an IEEE Senior Member, IEEE-CNSV member, past Chair of the Silicon Valley Chapter of the Engineering in Medicine and Biology Society, guest lecturer at the Univ. of Arizona Biomedical Engineering department, and a member of OSA, APS, SPIE and Sigma Xi. He has over 30 scientific publications and U.S. / International presentations of research, has reviewed text books for the Springer Series in Optical Sciences, and has been a peer reviewer for several journals including Lasers in Surgery and Medicine, Optics Express, and Optics Communications.