OPTICAL COHERENCE TOMOGRAPHY

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Optical coherence tomography (OCT) has become a critical imaging tool in medicine owing to its non-invasive imaging capability of tissues with micrometer-level details. From its initial experiments in the 1980s to now, the adoption of OCT has been facilitated not only by scientific innovations but also advances in fiber optic telecommunications and photonics, as well as industry and government support. This review highlights key milestones that have contributed to the clinical adoption of OCT, as well as current and future trends.

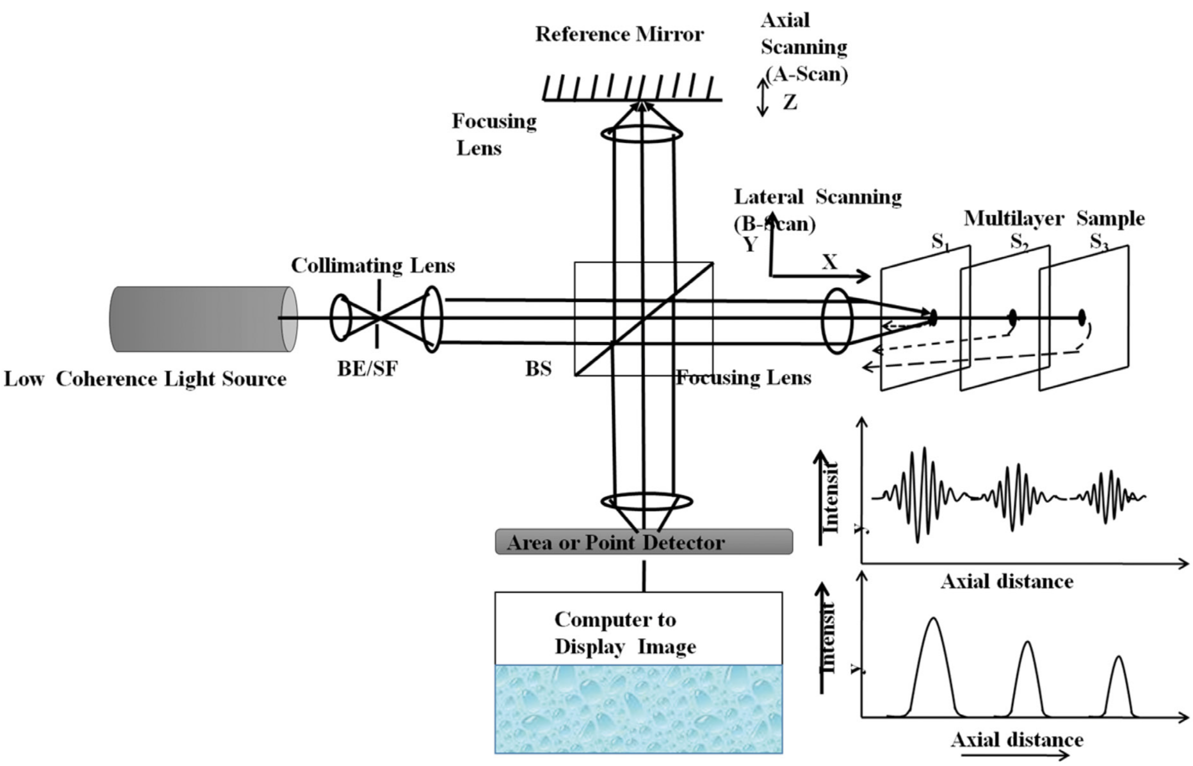
Optical coherence tomography (OCT) represents one of the major imaging technological breakthroughs of our century, owing to its capabilities to noninvasively enable three dimensional (3D) visualization of tissues in living specimens with cellular-level resolution [1]. OCT has become the standard of care in ophthalmology and has been a critical tool for understanding disease mechanism, facilitating their diagnosis, and monitoring their treatment, particularly for blinding diseases such as diabetic retinopathy, age-related macular degeneration (AMD), and glaucoma, affecting hundreds of millions of people worldwide. OCT has also emerged as a critical clinical tool in cardiology, dermatology, endoscopy, gastroenterology, and beyond.

The principle of OCT is analogous to ultrasound imaging, measuring the time of flight of echoes reflecting from different layers of tissues to infer the depth localization of the layers. Owing to the greater speed of light waves compared with ultrasound waves, OCT leverages the unique sensitivity of interferometry techniques to achieve such measurements. Interferometry can be traced back to Thomas Young's double-slit experiment in the 1800s, where two light waves from the same source, passing through two distinct slits, can be recombined coherently. The resulting wave has a maximum energy (i.e., constructive interference) when the difference in distances travelled (i.e., the optical path difference) by the two waves is a multiple of the wavelength (i.e., the waves are in phase) and a lower energy (i.e., destructive interference) when the optical path difference between the two waves is an odd multiple of half the wavelength (i.e., the waves are out of phase). By analysing the repeated pattern (i.e., fringes) of the interference signal, one can inform the distance travelled by one wave relative to the other, with an accuracy below the wavelength of light. The same principle is applied to different variations of interferometry techniques and OCT, with one light path serving as the reference arm and the other path serving as the sample arm.

While several scientific experiments, including Albert Michelson's interferometry in the 1880s and low-coherence interferometry (LCI) by Sir Isaac Newton in the 1980s, have contributed to the working principle of OCT, pioneering experiments carried out by Professor Adolf Fercher's group at The Institute of Medical Physics (IMP), Medical University of Vienna and Professor James Fujimoto's group at Massachusetts Institute of Technology (MIT) were instrumental to the commercial development and clinical utility of OCT. Professor Fercher's group demonstrated the first measurement of the axial length of a living human eye using LCI in 1986 [2], enabling the development of the first commercial ocular biometry system for measuring intraocular distances, which has been critical for the management of cataract. On the other hand, Professor Fujimoto's team advanced the development of femtosecond lasers in medicine, leading to the first demonstration of OCT for imaging the eye in 1991 [1] and the launching of the first commercial OCT system by Zeiss in 1996. Among several prizes, the two teams were jointly awarded the 2017 Russ Prize by the United States National Academy of Engineering for their invention of OCT and its tremendous impact in clinical care, and especially in ophthalmology (Figure 1).

PRINCIPLE OF LOW COHERENCE INTERFEROMETRY AND OPTICAL COHERENCE TOMOGRAPHY

The principle of low coherence interferometry (LCI), from which OCT derives, leverages the fact that for a broadband source with multiple wavelengths, light reflecting from a given layer of the sample interferes constructively (i.e., maximum energy) with light reflecting from the reference mirror at all the wavelengths only when the location of the layer exactly matches that of the reference mirror, forming a strong peak (i.e., the sum of energies at all wavelengths). For any other layers of the sample, the mismatch with the reference mirror causes all the wavelengths to be out of phase with each other, thereby interfering destructively (i.e., cancelling out their energies). The reflectivity profile therefore has a single peak corresponding to the location of the layer. The broader the source, the more define the location of the layer, which characterizes the axial resolution of the OCT system. The same process can be repeated for individual layers of the sample by scanning the location of the reference mirror to match that of individual layers of the sample, as illustrated below.



Principle of Optical Coherence Tomography. Courtesy of Prof. D.S. Metha.

Figure 1. The 2017 Russ Prize honoring the teams of Professors Fujimoto from the Massachusetts Institute of Technology (MIT) and Fercher from the Institute of Medical Physics (IMP), Medical University of Vienna, for their pioneering experiments in OCT. Adapted with permission from The National Academy of Engineering.

Over the three decades that followed, several technologic breakthroughs have significantly contributed to the clinical utility of OCT and its broader adoption in a multitude of medical fields.

Major milestones in the development of OCT

OCT has evolved from its initial inception using the time delay between the reference arm and the sample arm, known as time-domain OCT (TD-OCT), to its advanced approach known as Fourier-domain OCT (FD-OCT) in which the interference between light reflecting from all layers of the sample and the reference arm can be registered separately for individual wavelengths. By combining this information from all wavelengths of the source and performing the Fourier analysis of the spectrum, one can decode the reflectivity strength of individual layers, defined as amplitude scan (A-scan), thereby forming the basis for the 3D image reconstruction in FD-OCT. This concept was first introduced by Fercher *et al.* in 1995 [3] and was later developed into two approaches: the first approach, termed spectral-domain OCT (SD-OCT), using a line-camera to simultaneously register all wavelengths of the source (i.e., the interference spectrum) [4]; and the second approach, termed sweep-source OCT (SS-OCT), in which individual wavelengths are registered sequentially using a point detector and the full interference spectrum is achieved by sweeping across individual wavelengths of the source [5]. It is worth noting that the clinical adoption of TD-OCT systems was challenging (Zeiss, who was the first company to commercialize OCT systems almost abandoned this market segment) until the advantageous imaging sensitivity and speed of FD-OCT over the state-of-the-art TD-OCT was demonstrated by Leitgeb *et al.* in 2003 [6], marking a paradigm shift in the field of OCT and contributing to its broader adoption in clinical care. It is also worth mentioning that while SD-OCT has enabled the finest depth sectioning of tissue by broadening the light source, SS-OCT has enabled the deepest penetration in tissues owing to its primary range of operation within the longer wavelengths as well as the fastest time-delayed based point recording of the interference spectrum. Also, the advanced version of TD-OCT known as full-field OCT (FF-OCT) has enabled the fastest enface visualization of different layers of tissues with a transverse resolution close to that of confocal microscopy.

Figure 2. Comparison between TD-OCT, SD-OCT, and SS-OCT. Adapted with permission from [1]; Rothenbuehler, S. P., Malmqvist, L., Belmouhand, M., Bjerager, J., Maloca, P. M., Larsen, M., & Hamann, S., Comparison of spectral-domain OCT versus swept-source OCT for the detection of deep optic disc Drusen. Diagnostics, 12(10), 2515 (2022); and Nathans, J., Seeing is believing: The development of optical coherence tomography. *Proceedings of the National Academy of Sciences*, 120(39), e2311129120 (2023).

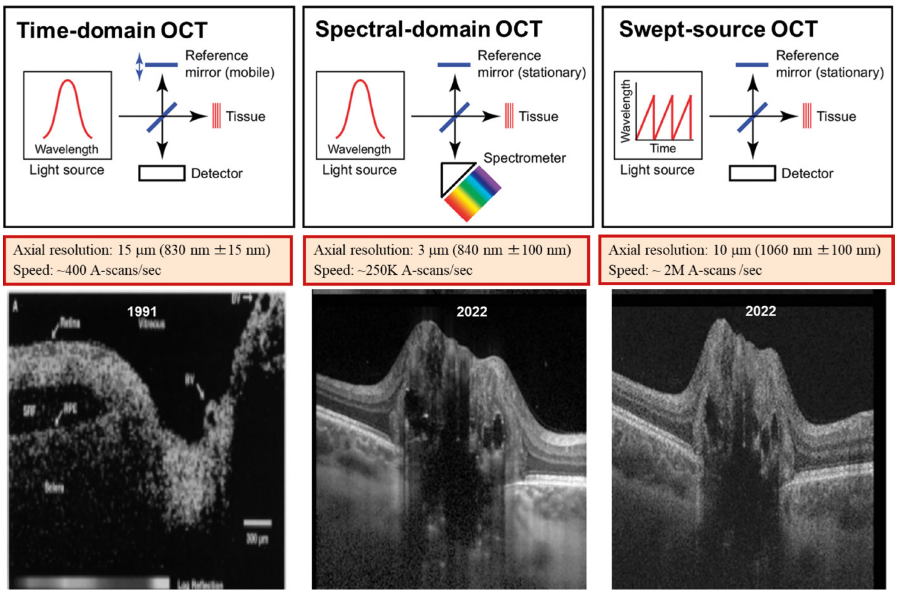


Figure 2 presents the three main configurations of OCT along with illustrations of their imaging capabilities.
Another major milestone in OCT was the introduction of OCT angiography (OCTA) for non-invasive assessment of vasculature in living tissues, which was up to then performed with the traditional invasive fluorescein angiography. While blood flow evaluation was first demonstrated using Doppler TD-OCT, the advanced imaging speed of FD-OCT had made possible fast volumetric imaging of tissues with repeated scans, enabling enface visualization of the vasculature network in the eye and brain [7]. This milestone provided another paradigm shift in the clinical utility of OCT, adding functional imaging capabilities to the structural OCT imaging modality, and enabling to assess disease progression and response to treatments such as anti-vascular endothelial growth factor (anti-VEGF) in a multitude of vascular retinal diseases, including diabetes retinopathy, age-related macular degeneration, and glaucoma.

Contribution of advanced technologies to OCT development

From TD-OCT to SD-OCT and SS-OCT, OCT owes its rapid development and adoption, not only to scientific innovations, but more importantly to advances in technologies such as fiber optic telecommunication, and photonics, including broadband sources, fast tunable sources, and sensitive detectors.

1. The development of single-mode fibers in the 1980s has enabled OCT systems to move from free-space interferometers using bulk optical components to fiber-based interferometers, yielding compact and stable imaging systems while also opening new opportunities for OCT integration into catheters and endoscopes.
2. OCT systems initially relied on ultrafast femtosecond lasers to achieve high axial resolution imaging, making OCT systems expensive and less user-friendly as femtosecond lasers are challenging to operate and maintain. The development of robust broadband superluminescent diode (SLD) light sources has enabled more compact and cost-effective systems, thereby facilitating the broader adoption and clinical utility of OCT.
3. The development of Fourier domain mode locking technologies for tuning SS-OCT sources as well as microelectromechanical systems vertical-cavity surface emitting laser (MEMS-VCSEL) have enabled SS-OCT to reach a multi-megahertz A-scans/sec speed, significantly boosting the development of intraoperative OCT and OCTA and their clinical utility.
4. While initial OCT systems relied on Silicon (Si) based charged couple device (CCD) detectors with limited sensitivity at longer wavelengths, the development and adoption of Indium Gallium Arsenide (InGaAs) based complementary metal-oxide-semiconductor (CMOS) detectors with higher sensitivity at longer wavelengths has enabled the expansion of OCT in imaging highly scattering tissues with improved light penetration and imaging depth.

Clinical Applications of OCT

OCT was initially developed using sources in the optical or first near-infrared (NIR-I) window (~650 – 900 nm) to primarily image the eye, owing to the almost transparent nature of eye tissues within that wavelength range, and making ophthalmology the primary field of application of OCT. OCT has become the standard of care in treating a multitude of eye disease conditions such as diabetic retinopathy, age-related macular degeneration (AMD), and glaucoma. OCT is also used for detecting and monitoring glaucoma progression by evaluating retinal nerve fiber layer thinning and optic nerve damage. In AMD in particular, OCT has played a major role in monitoring the progression and treatment response to intravitreal anti-VEGF therapy. However, highly scattering tissues such as skin were challenging to image owing to the limited penetration of light beyond a couple hundred of micrometers. The later development of broadband sources in the second near-infrared (NIR-II) window (~1000 – 1700 nm), enabling lower tissue scattering and deeper light penetration in highly scattering tissues, together with advanced technologic development in fiber optic telecommunication and photonics, has facilitated the adoption of OCT in other biomedical fields such as dermatology, dentistry, and beyond. Additionally, the integration of OCT into endoscopes and catheter probes has also opened new era of opportunities in endoscopy, cardiology, gastroenterology, urology, and neurology.

Current trends and outlook

Despite the rapid development and adoption of OCT in the past few decades, the technology still holds great potentials with further improvements not only in hardware and software, but also in clinical utilities through multidisciplinary collaborations of engineers, scientists, clinicians, and entrepreneurs. Hardware's improvements will be driven by new integrated technologies and photonics including broader and faster SS-OCT sources, faster and more sensitive detectors, to cite a few. The ongoing integration and adoption of machine learning and artificial intelligence (AI) into the OCT imaging pipeline, especially for processing and analysing data, will dominate the software sector, which will significantly enhance the clinical utility of OCT, allowing to detect diseases in the early stage, improving the diagnosis accuracy, and assisting with automated and real-time diagnostic and decision-making. Other ongoing efforts in OCT development are the integration of more functional imaging capabilities into OCT systems, including OCT elastography for biomechanical evaluation of tissues, polarization-sensitive OCT for evaluating the birefringence of tissues in normal and diseased conditions, OCT optoretinography for assessing light-evoked change in scattering properties and response of photoreceptors, dynamic OCT to enable label-free evaluation of cellular motility, to cite a few. Finally, the development of cost-effective miniaturized and portable OCT systems, including on-a-chip and smartphone-based OCT systems could boost the adoption of home- or community-based OCT systems,facilitating clinical care access to underserved rural areas and reducing patients' burden from frequent follow-up visits to the clinic.

Conclusion

This review provides a short summary of key milestones in the development of OCT that have contributed to its broader adoption in the medical field. The author would like to emphasize that while this review highlighted a few of the pioneering experiments in OCT, these innovations often built upon other scientific contributions, often at the boundaries of fields, which have significantly impacted the development of OCT. It is also important to highlight that the impact of OCT wouldn't be possible without the synergy of multidisciplinary collaborations of scientists, engineers, clinicians, and entrepreneurs, as well as the support of industry and governments. Looking forward, several areas of research and development, including optoretinography, parallel OCT, dynamic OCT, enface OCT, and others are underway and have the potential to expand the capabilities and application fields of OCT. Also, the strategic integration of IA into the OCT imaging pipeline is transforming the workflow in clinical practices.

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