Development of cellular resolution optical coherence tomography

Diagnosis of most mucosal diseases including epithelial cancers relies on white-light endoscopy / visual inspection followed by random biopsy and histology examination. These current standard of care tools are associated with many issues such as sampling errors, tissue destruction, complications, and processing artifacts. In addition, it is too traumatic to take a biopsy from tissues like eyes and coronary arteries. Being high resolution, high speed, and non-invasive, optical coherence tomography (OCT) has emerged as an endoscopic and intravascular imaging tool that provides valuable anatomic information complementary to the standard of care methods. It has a typical resolution of ~10 μm, which is too coarse for visualizing most cellular structures. Micro-optical coherence tomography (μOCT) provides spatial resolution of 1~2 μm to visualize microstructures at the cellular and sub-cellular level. Two of the major inherent issues with current μOCT imaging systems are the auto-correlation artifacts (ACA) and complex conjugate artifacts (CCA). ACAs originate from the interference between sample reflectors or scatters of different depths; CCA arises from the fact that the current OCT system can only detect the real part of the complex interferometric signal. Another inherent major issue with the current μOCT imaging systems is the limited depth of focus (DOF). The DOF, defined as the confocal parameter in the classical theory of Fourier domain OCT (FD-OCT), is proportional to the square of the transverse resolution. Consequently, a trade-off occurs between the transverse resolution and the DOF in which a lower transverse resolution results in a larger DOF and vice versa.

The main objective of this research is to develop novel optomechanical techniques and apparatus to overcome the above-mentioned issues with μOCT to facilitate its clinical applications.

Firstly, we develop a novel homemade dual-channel spectrometer by employing two lines of a three-line charge coupled device (CCD) to suppress ACA and CCA. For ACA suppression, two interferometric spectra with a phase difference of π are detected by the dual-channel spectrometer simultaneously. ACA is suppressed by counterbalance signals obtained from dual channels. For CCA suppression, two interferometric spectra with a phase difference of $2\pi/3$ are detected by the dual-channel spectrometer simultaneously. The complex interferometric signal is reconstructed by trigonometric manipulation of two real interferometric spectra, and then ACA is suppressed by use of inverse Fourier transform.

Secondly but more importantly, we develop a series of novel optomechanical techniques and apparatuses to address the fundamental problem of limited DOF in high-resolution μOCT. Multiple aperture synthesis (MAS) is a kind of digital refocusing technique, which is analogous to synthetic aperture radar (SAR). The key technology of MAS is the implementation of aperture division and the multiplexing apparatus. In the first place, a micro cylindrical lens drove by a piezoelectric transducer (PZT) is employed to demonstrate the feasibility of DOF extension without signal loss and sidelobe artifacts. In the second place, a mirror with two surfaces coated is employed to demonstrate the potential DOF extension for ocular and skin applications. In the third place, a birefringent calcite spacer is employed to demonstrate the potential of DOF extension for endoscopic and intravascular applications. In the fourth place, a technique named pixel reassignment, originally and broadly used in the confocal microscopy, is also developed and applied in desktop FD-OCT to moderately improve the overall performance. The proposed MAS

technique overcomes the inherent trade-off between DOF extension and signal loss/sidelobe artifacts and may ultimately overcome the DOF limitation in high-resolution μOCT.

The problems of limited DOF and ACA and CCA are addressed in this thesis, which enables us to visualize imperceptible changes in cellular and sub-cellular resolution, and evaluates pathological lesion in an early period by characterizing the cellular and sub-cellular morphology of human tissues. All the novelties enable this project to play a potential role in the clinical practice of disease diagnosis and treatment, especially for gastrointestinal cancer, epithelial cancer, and atherosclerosis.