Developing polarization sensitive Micro optical coherence tomography – towards high contrast, resolution and sensitivity optical biomedical imaging

Optical coherence tomography (OCT) is an interferometric three-dimensional imaging technique. Thanks to its non-ionizing near-infrared light source, backscattering detection configuration, depth-resolved image formation, as well as high imaging resolution, sensitivity and speed, OCT is perfectly suitable for in vivo medical diagnosis. OCT has been developed into a standard diagnostic device in ophthalmology, meanwhile, its applications on cardiology, endoscopy and dermatology has received intensive investigation and are now entering the pre-clinical stage.

Micro optical coherence tomography (μOCT) is an OCT variant that pushes the resolution of conventional OCT to the micrometer level. With around 1-μm resolution, μOCT can visualize biological tissues at the cellular and sub-cellular level, and promises to provide cellular pathological behavior information, which is important in the diagnosis and treatment of various diseases, including the ultra-early detection of cancer. Standard OCT image, formed from the intensity of backscattered light, provides only the morphology information, thereby lacking the specificity to distinguish structures with similar scattering property. Some biological tissues such as muscle, collagen, tendon or stressed connective structures are birefringent. Polarization sensitive OCT (PS-OCT) adds the birefringence contrast to standard OCT image by employing the polarization diverse detection. The local birefringence map of a tissue is extracted from the depth evolving polarization state, result of the light-tissue interaction. The marriage of μOCT and PS-OCT is expected to bring new possibilities and opportunities by visualizing the birefringence property of sub-cellular structure, such as cilia and micro-tubes in trachea epithelium and cell multiplication.

However, challenges exist in the construction of a PS-μOCT. PS-OCT needs two different polarization states illuminating on the same sample spot to solve the local birefringence properties, specifically, local retardation and local relative optic axis. Currently main PS-OCT uses a polarization modulator to change the polarization state of adjacent A-scan lines, or encodes various polarization detections on different imaging depth. However, these methods are not applicable for high resolution OCT. The bandwidth of a modulator limits the system resolution lower than 5 μm. The depth range of an OCT is determined by the wavelength resolution of the spectral detection. For μOCT with an ultra-broadband source, there are little margins left for extra depth multiplexing. To overcome this problem, this thesis describes a new reasoning methodology, derived from the polarization optical reversible theorem, termed as “conjugate point reason”. This reasoning theorem states that, for a sample with random birefringence layer structure (no diattenuation), the backscattered polarization state evolving along the depth is consisted discontinuous arcs lying on the Poincare sphere. In a transpose-symmetric system, the circles that the arcs are on all pass through the “conjugate point”, which is the Q-U plane reflection of the input polarization state. In the first chapter of this thesis, I describe both the experiments and theoretical confirmation of this reasoning theorem. Furthermore, this reasoning technique enables the single input PS-OCT to resolve local birefringence properties, open a way towards the construction of a PS-μOCT. In this chapter, the prototype of a PS-μOCT based on conjugate point reasoning is demonstrated.

There are other practical difficulties hindering a realization of the clinical viable PS-μOCT system. The PS signal is sensitive to speckle noise, sample birefringence and fiber polarization mode dispersion (PMD). In the second chapter, I compared different averaging strategies and found that averaging in full Stokes space delivers the optimal accuracy. In another aspect, it's inevitable to use single mode fiber in an OCT system. It can be demonstrated that a piece of single mode fiber with 1 m length hold in a reel can introduce a polarization mode dispersion (PMD) of around 5 fs, corresponding to optical path length of 1.5 μm, enough to destroy the polarization detection in μOCT. In addition, PMD is extremely sensitive to temperature and fiber movement, thus difficult to correct. The third chapter of the thesis discusses the degradation of PMD on PS-μOCT detection accuracy and, to my best attempt, develops a method to correct the PMD.

Collaborating with one of the leading research groups in PS-OCT, I developed an approach to fabricate a tissue-like OCT birefringence target, the key part of the protocol for characterizing and calibrating the absolute detection value, sensitivity and range of PS-OCT. Taking use of the stress-induced birefringence, the leveled birefringence regions were created by stretching the polycarbonate sheet to different lengths. Several pieces of polycarbonate sheet with different birefringence and different patterns were fabricated. To package up the target, the birefringent sample pieces were embedded into matrix made of epoxy. Scatters were added into the polycarbonate and epoxy to mimic the scattering property of the biological tissue. The fabrication, test and demarcation of the target are described in the fourth chapter.

Besides from polarization detection, to maintain and improve the resolution of μOCT, I developed a spectral estimation (SE-OCT) algorithm to super-resolve the layer structures in transparent samples. This algorithm extrapolates the interferometric fringes outside the source bandwidth, thereby improving the resolving ability of OCT. Based on the assumption that the sample was consisted of sparse layers, the algorithm can super resolve two close surfaces within 200 nm, far under the physical resolution. SE-OCT shows good performance in transparent tissues such as corneal. In addition, I discussed the detailed dispersion correction methods for unbalanced reference and sample optical paths, including the influence of remaining uncorrectable dispersion, such as PMD.

In this thesis, a method to improve the sensitivity of spectral domain OCT is also included. Termed as spectral encoded extended source OCT (SEES-OCT), this new configuration is an attempt to improve signal strength for ophthalmic imaging. By introducing a dispersive element in the infinity space of the sample arm, the scanning laser spot was dispersed with a visual angle of 7.9 mrad. The maximum permissible exposure (MPE) of such an extended source is 3.1 times larger than that of a "standard" point source OCT, which corresponds to sensitivity improvement of 5 dB. The advantage of SEES-OCT in providing superior penetration depth over a point source system was demonstrated.

In conclusion, this thesis provides a step forward to construct a viable PS-μOCT with high resolution, sensitivity and contrast. Several technical problems were discussed and addressed with my best attempt. The feasibility and effectiveness of the proposed solutions were demonstrated with phantoms and ex vivo animal imaging in the context of relevant biological diseases.