Endoscopic structural and molecular optical imaging

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Chapter 8 |

Summary

In the past centuries, medicine has become more quantitative by including accurate tests of measurable quantities (*e.g.*, measuring temperature and chemical analysis of body fluids) to diagnose and assess patients. Nevertheless, visual inspection is still and will probably always be a prime form of medical assessment. Limited by scattering and absorption of light into tissue, visual investigation can only provide information originating from the very first layers of the human body. Allowing doctors to see within the human body in a minimally invasive manner, medical imaging has revolutionized the medical practice with methods such as magnetic resonance imaging (MRI) and X-ray computed tomography (CT) now being routine exams in hospitals throughout the world.

Optical imaging (*e.g.*, microscopy, photography) can reveal details in biological tissue with a spatial resolution of 1-100 μm (about 10-100 times better than MRI and CT); however, it suffers from the same limitations of visual inspection: an imaging depth limited by the scattering and absorption of light in tissue. Endoscopes are medical devices formed by a tube and a lens that circumvent this limitation by producing light-based images of internal organs accessed through an orifice or a small incision.

Optical coherence tomography (OCT) is an interferometric optical imaging technique that creates three-dimensional images of tissue based on its light scattering properties. The functionality of OCT can be extended beyond its primary role of 3D tissue imaging, to, *e.g.*, reveal blood flow, highlight birefringent structures, and measure the attenuation coefficient of tissue. Polarization-sensitive OCT (PS-OCT) is an extension of OCT that measures how a sample affects the light polarization state. Several types of tissue with fiber-like structures (*e.g.*, smooth muscle and collagen) exhibit form birefringence, which induces a time delay between light propagating with different states of polarization. By measuring the time delay accumulated between orthogonal polarization states during propagation in the tissue, it is possible to reconstruct the tissue birefringence and therefore highlight the presence of particular types of tissue in the sample. Dynamic OCT (DOCT) reveals the presence of blood flow by determining nanometer-scale displacements of scatterers (in this case, red blood cells) within the tissue between consecutive scans. Attenuation coefficient (AC) imaging has been explored as a means to obtain quantitative information from OCT images by

determining the light attenuation power of the examined tissue, which would allow to highlight the presence of a tissue type specifically.

This thesis presents the development of a PS-OCT motorized endoscope for lung airway imaging. The polarization mode dispersion (PMD) of the PS-OCT system is characterized and compensated. A metric that highlights the presence of uniformly arranged fibers in the tissue is used for the first time in lung tissue to reveal the presence of airway smooth muscle (ASM). A novel segmentation algorithm is developed to precisely segment the surface of the endoscope and of the airway lumen, which is needed for the PMD processing step and to improve the visualization of the relevant portion of the images. Chapter 3 presents PS-OCT images acquired *in vivo* from a porcine lung to demonstrate that the system is safe for clinical use. Chapter 4 displays endoscopic airway images of a human patient who has severe asthma to show the ability of PS-OCT of highlighting the presence of ASM in the airway wall, which is a key parameter of tissue remodeling. Attenuation coefficient OCT images of the airway wall are shown for the first time, correcting for artifacts present in traditional OCT images and showing improved contrast for epithelial folds in the airway lumen and structures located deep in the cross-sectional scans. DOCT images reveal the presence of blood flow in the airway wall, potentially helping to diagnose the patient. The PS-OCT endoscopic system promises to be an ideal tool to assess tissue remodeling in asthma patients in a minimally invasive manner.

The PS-OCT setup has also been used to investigate scars caused by burn wounds on the skin of five patients imaged with a custom handheld scanner, as shown in Chapter 6. The quantification of the tissue birefringence correlates with the density of the collagen fibers measured from histological slides of biopsies acquired from the same area, suggesting that PS-OCT may be used to follow and predict the evolution of scarred tissue caused by burn wounds.

Nevertheless, (PS-)OCT is not able to retrieve molecular information from tissue and is therefore not able to specifically reveal the presence of a cell type of interest. With the emergence of targeted tumor therapies, such as immunotherapies, there is an increasing need of studying the tumor microenvironment in detail, to understand the mechanisms at the base of the immune response. Targeted fluorescence, in the form of immuno-near-infrared fluorescence (immuno-NIRF), can specifically highlight the presence of a particular cell type by targeting its receptor with an antibody labeled with a fluorescent molecule.

In Chapter 5, a dedicated immuno-NIRF module has been combined with the OCT setup using double-clad optical fibers (DCF) to retrieve molecular and architectural information from biological tissue. Images of tumors obtained from a mouse model demonstrate the ability of the immuno-NIRF-OCT system to perform imaging with a DCF-based handheld scanner and with a custom DCF endoscope. The immuno-NIRF and OCT images reveal that the tumor microenvironment is highly heterogeneous. Immuno-NIRF images show that the cancer cells are non-uniformly distributed while OCT images show the presence of other structures such as the stroma and fatty cells. The system allows studying the tumor microenvironment at a resolution of about 10 µm, which is about 100 times better than the current clinical practice, represented by positron emission tomography. This study suggests that immuno-NIRF-OCT is an ideal tool to study in detail the microenvironment of tumors located near the surface of the lumen of internal organs such as the esophagus or the lungs.

Finally, Chapter 7 presents an overview of the thesis and discusses future directions to continue the work presented.