Clinical applications of functional optical coherence tomography

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GENERAL INTRODUCTION

- CHAPTER 1 -

Imaging the human body has been of interest since the dawn of modern medicine. In today's clinical practice, monitoring and imaging techniques are indispensable in disease management. A variety of technologies has been developed over time, covering a large part of the electromagnetic spectrum. When these technologies are categorized in terms of imaging depth versus resolution, it can be quickly seen that all these technologies suffer from fundamental limitations coming from an apparent inverse relationship between depth and resolution (figure 1-1).

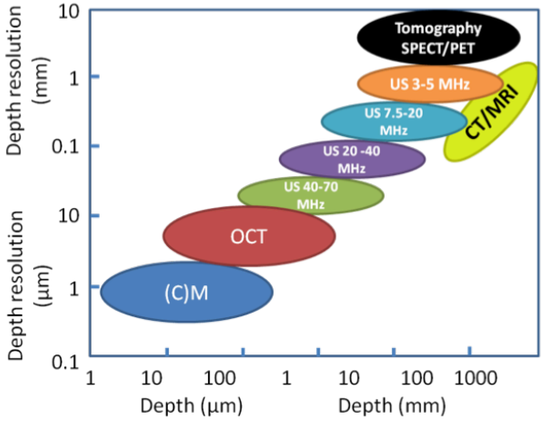

Fig 1-1: An overview of most available imaging technologies. A trade-off is visible between Imaging depth and resolution. Optical Coherence Tomography (OCT) is depicted in red filling the gap between microscopy modalities and the other techniques.

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) both use radiation from radio nuclides which, after distribution through the human body, result in whole organ imaging with high contrast. Imaging modalities like magnetic resonance imaging (MRI) and computed tomography (CT) are also responsible for imaging tissue morphology and, in case of MRI, local functionality due to high sensitivity to water in tissue. These techniques are followed by a range of ultrasound (US) modalities. Ultrasound imaging has the capability to visualize tissue with a relatively high resolution (~100 µm) and depth (~10 cm), but is limited in applicability because it needs contact with the sample under study.[1]

The invention of the light microscope by Antonie van Leeuwenhoek made it possible to image tissue down to the cellular level. With lenses and mirrors, the microscope equipped scientists with an instrument to study samples at an unprecedented level. Depending on the wavelength used, diffraction limited resolutions can be obtained of 2 to 1 µm. However, imaging depth is limited due to absorption and scattering of the imaged tissue sample. These numbers on resolution were stretched to approximately 0.4 µm due to the invention of the confocal microscope, which uses point illumination and point detection (by means of pinholes) to eliminate detection of out-of-focus light which becomes more predominant when deeper tissue structures are visualized. [2]

The resolution/imaging-depth gap between high resolution ultrasound modalities and the (confocal) microscope has not been filled until the invention of optical coherence tomography (OCT) in 1991. [3] At this time, it emerged as a promising technology using backscattered light for three-dimensional imaging of retinal tissue by offering high transversal and axial resolution (< 10 µm) with an imaging depth of approximately 2 mm.

From the moment that OCT saw its first light, it was quickly realized by both researchers and physicians that this technology could have a major contribution in the field of Ophthalmology given the transparent nature of the eye. It is therefore no surprise that almost 50 percent of all peer reviewed publications in OCT to date are on clinical applications of imaging the eye, as depicted in figure 1-2 (2013 Thomson Reuters). The first OCT systems were all operating in the near infrared region at 800 nm were water absorption is close to zero (see also figure 1-3). Detailed descriptions are now available of the morphology of the cornea and retina and even physiological functions are studied with OCT.[4] Another vast field of the research originated from a technological point of view with great emphasis on imaging speed, resolution (associated with different wavelength regions) and design of smart in vivo and ex vivo machine-patient interfaces. The latter has led to an increase of imaging on the inside of the human body, since small sized, smart catheter interfaces are more and more developed.[5] Today, several clinical OCT systems are commercially available for ophthal

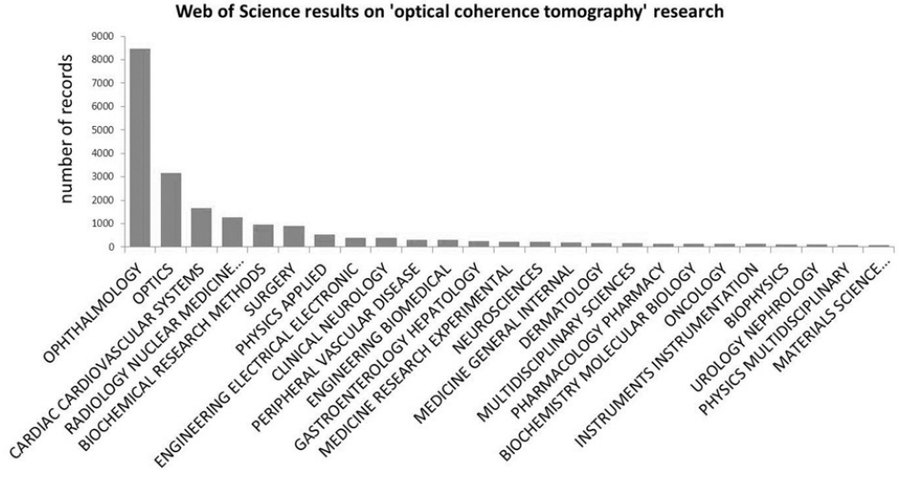

Fig. 1-2 All peer reviewed publications in OCT to date (2013 Thomson Reuters)

mological and cardiovascular imaging applications. All in all, OCT is becoming increasingly available for different clinical settings ranging from ophthalmology to cell biology.[6]

Next to morphological imaging, information on the physiological function of tissue can be derived from the OCT signal. Several functional extensions to OCT imaging are proposed and researched over the years. This research area investigates the origin of the OCT signal, covering the physics of scattering and absorption and phase sensitivity that includes polarization sensitivity, Doppler shift and speckle. Understanding and quantification of these principles based on known optical and electronic properties of the used OCT system, and the optical and mechanical properties of the material under study, will define OCT as a powerful tool in medical diagnostics.[7]

1.1 THESIS MOTIVATION AND AIM

OCT has great potential as an optical biopsy tool because the images resemble architectural similarities to normal histology. Moreover, physical properties such as refractive index, Brownian motion of cells and/or cell organelles, orientation, organization, size and phase function of tissue scatterers are parameters that play a major role in light scattering of tissue and is related to biological condition of tissue or cells.

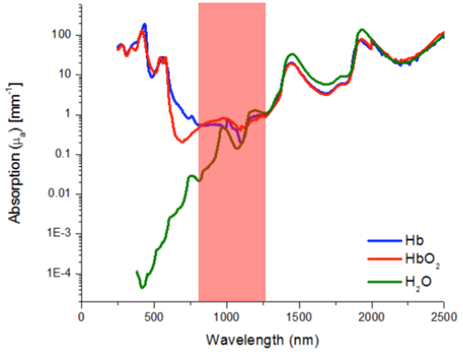

Fig. 1-3: Graph showing absorption coefficients (μ_a) vs. Wavelength of some important tissue absorbers such as water, oxygenized and de-oxygenized blood. Note that absorption from 800 up to 1300 nm, the so called tissue optical window, is relatively low.

Throughout this thesis, OCT is explored to extract quantitative light scattering properties from OCT data by means of the optical attenuation of light. The attenuation coefficient μ_{oct}, [mm^{-1}], describes the decay of the detected OCT signal as deeper structures are probed and is intimately related to the organization of the measured tissue. The attenuation coefficient is the sum of the absorption and scattering coefficients, where the former is determined by the concentrations of light absorbing chromophores in the measurement volume, whereas the latter reflects size- and refractive index distributions of the different tissue constituents. Because the progress of many diseases is accompanied by changes in these distributions (both intra- and extra-cellular), light scattering techniques have great potential as monitoring and diagnostic tools – OCT especially so because it allows highly localized quantitative analysis of these scattering properties. The viability and limitations of this approach are first tested in a tissue-simulating 'phantom' environment and studied in-vitro by monitoring cell death in retinal pigment epithelial cells, processes that are well known to be accompanied by intracellular changes. From a practical perspective, the attenuation coefficient of tissues at 800 nm were most ophthalmic systems operate is rather high (typically 5-20 mm^{-1}) and limits imaging depth. To overcome this limitation, we developed one of the first swept source laser systems which operates at 1050 nm, and furthermore used commercially available OCT systems operating around 1300 nm. To assess clinical relevance of our approach, several applications are studied using functional OCT attenuation mapping at 800 and 1300 nm with a main emphasis on the differentiation of tumorous from normal tissue.

The aim of the work presented in this thesis is to show the potential of functional OCT to discriminate pathological from normal tissues in several clinical settings, by means of the attenuation coefficient. To that end, several fundamental studies are carried out to increase the fundamental understanding of the measured signals (in phantoms, during apoptosis) and both ex and in vivo investigations are performed in the urological and gynecological clinic.

1.2 THESIS STRUCTURE

In this thesis, an exhibit is given in chapter 2 on OCT, were all systems are described that are used throughout the thesis. Additionally, functional extensions of OCT enabling quantitative measurement of local scattering properties are also described in chapter 2. A brief overview is given in Chapter 3 on the development of optical phantoms as test and calibration tool for (functional) OCT systems. The use of optical phantoms as calibration tool for commercially available ophthalmic OCT systems is studied in chapter 4. Other than in phantoms, changes in light scattering are induced by fundamental changes in cellular properties such as apoptosis (programmed cell death) or carcinogenesis (development of cancer). We show in chapter 5 that induced apoptosis in cells in vitro give changes to light scattering which we quantify with functional OCT. In chapter 6, Swept Source OCT operating at a wavelength of 1050 nm is discussed and prototypically used for the improved detection of age related macular degeneration. Chapter 7, 8 and 9 describe urological applications of functional OCT, ranging from ex vivo grading of bladder cancer to the differentiation of kidney cancer ex vivo and the application of in vivo endoscopic OCT during renal surgery. Chapter 10 applies our procedure to gynecologi-

cal pre-cancerous lesions known as vulvar neoplastic tissue. Finally, a summary is given in chapter 11 , concluding remarks in chapter 12 and an outlook in chapter 13.

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