From sample structure to optical properties and back

A theoretical framework for quantitative OCT and its clinical application

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CHAPTER 7

Discussion and future perspectives

Optical coherence tomography (OCT) uses near infrared light to non-invasively acquire 3D images of biological tissue, with a resolution in the range of 5-15 µm and an imaging depth of approximately 2 mm. OCT can be a useful clinical tool for minimally invasive, high-resolution imaging of tissue structures and morphology.[1] In addition to morphological imaging, quantification of scattering properties from OCT images is a potential complementary source of information on microscopic tissue properties, which can be used clinically for tissue characterization.[2] These quantitative scattering parameters are: the backscattering coefficient ($\mu_{B,NA}$), which is a measure for the backscattered signal integrated over the detection numerical aperture of the system, and can be extracted from the OCT amplitude after careful calibration; the attenuation coefficient (μ_{OCT}), which quantifies the decay of the OCT signal in depth and is related to the scattering coefficient (μ_S); and the speckle distribution: the statistical distribution of voxel-to-voxel amplitude fluctuations inherent in the OCT signal, which is related to sub-resolution sample properties. All of these parameters can be extracted from OCT data using an appropriate model for the OCT signal. A large number of studies have been dedicated to such quantitative analysis of OCT data to address clinical questions, mostly concerning tissue characterization.[2] Many of these studies on *ex vivo* and *in vivo* tissues show promising results, indicating that these parameters are sensitive to differences in sub-resolution tissue structure and organization. However, the extracted quantitative parameters strongly depend on the applied methodology, and are sensitive to the selected input parameters. In order to establish the clinical value of quantitative OCT, the extracted parameters should be reliable and robust. Furthermore, the sensitivity of these parameters to clinically relevant changes in tissue should be determined. In this thesis a model describing the OCT signal and the relation of quantitative OCT-parameters (amplitude, attenuation coefficient and speckle distribution) to sample properties of discrete random media (size, refractive index and organization) is derived and validated. Furthermore, a robust method is presented to extract quantitative OCT-parameters from OCT data, which then are related to structural tissue properties and flow.

In the first part of this thesis (chapter 2 and 3) we have derived and validated a model for the OCT signal for discrete random media DRM. DRM are randomly positioned identical spherical particles for which calculations of the scattering properties are straightforward, thereby allowing accurate study of the influence of sample properties and system properties on the OCT signal. Chapter 4 is a review on the research investigating the use of μ_{OCT} for clinical application. In the latter part of this thesis (chapter 5 and 6) the findings of the first two chapters are applied in two *in vivo* pilot studies on the feasibility of quantitative OCT during surgery. Both studies are clinical examples in which non-invasive intraoperative imaging could be a valuable aid to the surgical practice. The main findings and discussions per chapter are discussed below, followed by general discussion and suggestions for future research.

In **chapter 2** a theoretical derivation of the OCT signal amplitude, and speckle distri-
bution is given for mono-disperse and homogeneous DRM, assuming single scattering.
Through this derivation quantitative OCT parameters (attenuation coefficient and speckle
variance) are expressed in terms of sample properties (particle size and concentration).
The model-based predictions are validated with experimentally obtained quantitative
parameters (attenuation coefficient and speckle variance) from OCT data of silica micro-
beads in water. Figure 1 shows theoretical predictions of sample scattering properties (μ_S,
$\mu_{B.,NA}$, and anisotropy) as a function of particle diameter and volume fraction of particles
with a refractive index of 1.425 in water (n=1.324) at an illumination wavelength of 1300
nm. The graph shows that scattering parameters μ_S, $\mu_{B.,NA}$ and anisotropy do not increase
linearly with particle concentration. The periodic Mie oscillations are clearly visible in the
$\mu_{B,NA}$ calculated curves. Such predictions forge a better understanding of the relationship
between sample properties and sample optical properties and can be useful in design
of experiments.
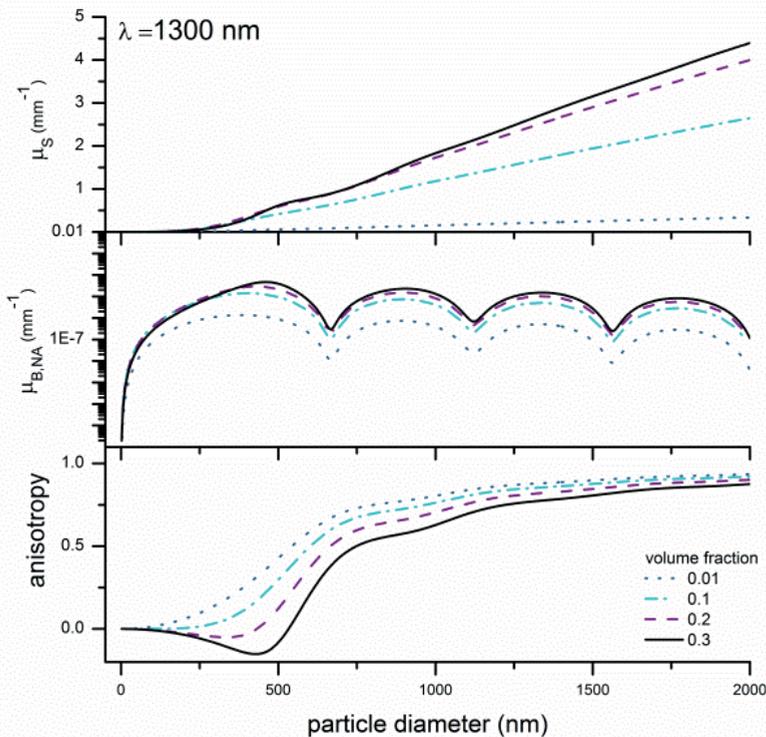
Figure 1. Calculated scattering properties (μ_s, μ_{bna}, anisotropy) as a function of particle diameter for
volume fractions ranging from 0.01, 0.1, 0.2 and 0.3. These calculations are based on a combination
of Mie theory with the Percus-Yevick structure factor with the following input parameters: illumina-
tion wavelength of 1300 nm with a bandwidth of 100 nm, refractive index of the particles of silica
microbeads 1.425 and the refractive index of the medium was set equal to that of water 1.324.

Chapter 4 is a literature review on the research towards the clinical application of μ_{OCT}. Models and methods to extract μ_{OCT} from OCT data as well as the μ_{OCT} values obtained in various clinically relevant tissue samples are summarized. We found that most studies are restricted to small sample sizes and are performed on *ex vivo* samples. The overview of the obtained results suggests that most pathologies show a change in μ_{OCT}, however not always significant. While in some studies relative μ_{OCT} values provide added contrast, other studies combine μ_{OCT} with other OCT-derived parameters to obtain significant difference healthy and diseased tissue. Furthermore, a wide spread in the obtained μ_{OCT} values is observed, which can be understood as a result of the use of different OCT systems, different methodologies to extract μ_{OCT} from OCT data, and different sample preparations. Multiple methods describing the OCT signal are available ranging in sophistication. From the results presented in this review it is concluded that standardization is crucial for further research and consensus on an appropriate model describing the OCT signal and correction for system parameters is needed.

In **chapter 5** the feasibility of the application of quantitative OCT during glioma resection was investigated in a pilot study in 5 patients. For quantitative analysis, we have developed a robust and automated data analysis pipeline to extract μ_{OCT} and speckle contrast values from the OCT data, which was validated using calibration samples. We conclude that the proposed method for quantitative *in vivo* OCT of the brain cortex is feasible during glioma resection surgery. However, applicability in subcortical areas is limited due to surgical restrictions and current probe sizes, causing low data quality. While the found μ_{OCT} values are close to the previously reported study on *ex vivo* brain tissue samples, further studies in which *in vivo* OCT scans and gold standard histopathology are matched as close as possible are needed to investigate the value of μ_{OCT} as a tool to discriminate between glioma and normal brain tissue. For improved clinical applicability a dedicated probe design is recommended. Furthermore, for real time analysis it should be considered that irregular tissue structures present in *in vivo* collected OCT data complicate analysis steps such as edge detection and ROI selection, which at the moment are managed by human supervision.

Chapter 6 presents the first study that demonstrates the feasibility of *in vivo* OCT imaging and flow detection in the reconstructed gastric tube during surgery in esophageal cancer patients. Here, the feasibility of intraoperative OCT imaging of gastric tissue and microcirculation is shown. Regions of flow could be distinguished from static tissue by calculating the speckle contrast in M-mode scans. By comparing OCT data with HE-stained histopathology slides, we were able to identify and verify tissue layers (serosal, subserosal, muscularis propria) and the location of the blood vessels. Also, lymphatic vessels were visible in both histopathology slides and OCT images, assuming that the lymph fluid is a weakly scattering medium. The percentage of pixels distinguished as flow was quantified in the M-mode OCT images as an objective parameter. This parameter

can potentially be used to differentiate normal from decreased perfusion areas. Possibly, surgeons could use a threshold value for quantitative assessment of the perfusion state of tissue and with that improve patient outcome. More research is needed towards this goal.

In summary, we have theoretically derived the OCT signal (amplitude and speckle distribution) for DRM, assuming single scattering. We have proposed a comprehensive model to extract quantitative OCT parameters from OCT images, which we have validated using controlled samples of microbeads in water. Furthermore, we were able to demonstrate the feasibility of quantitative OCT toward tissue characterization during glioma resection surgery and to detect blood flow in reconstructive gastric tube surgery. The limitations and challenges identified in these studies are discussed below and concluded with suggestions for future research.

REQUIREMENTS FOR SUCCESSFUL CLINICAL APPLICATION OF μ_{OCT}

A consensus on the model and method used to extract quantitative parameters from OCT images is needed in order to move towards clinical application of quantitative OCT. Sufficiently accurate knowledge of the system parameters and data output format of the OCT system are needed to ensure the use of the correct description of the OCT signal (e.g., amplitude, intensity or dB). Calibration of the OCT system, probe and validation of the analysis method can be performed using calibrated samples with known optical properties, which also can be used to quantify accuracy and reproducibility of the obtained results. Open source data analysis software, sample preparation guidelines and OCT data sets could be helpful in the standardization of the data analysis.

For various clinical applications, fast analysis and real-time visualization of μ_{OCT} maps are desirable. Therefore an automated and unsupervised analysis pipeline is required to deal with large amounts of data and to avoid human biases. Moreover, collection of *in vivo* and intraoperative OCT data introduces challenges concerning the quality of the OCT data. In chapter 5 and 6 respectively only 55 % and 45 % of the collected OCT data sets were suitable for quantitative analysis. Dedicated and study-specific probe designs and scanning protocols will significantly increase the quality of the OCT data. Furthermore, tissue irregularities and motion artifacts render data processing steps such as edge detection and region of interest (ROI) selection, necessitating human supervision of the analysis. Additional segmentation and image analysis steps could be added in future research to provide fully automatic analysis of *in vivo* OCT data.

In order to determine the added clinical value of the quantitative analysis of the OCT images, comparison with the current clinical gold standard, which in many cases

is histopathology, is needed. Matching of OCT data with histopathology can be very challenging. Recent studies show progress in matching of *ex vivo* OCT images and quantitative outcomes with histopathology.[3] However, matching *in vivo* OCT data with histopathological slides introduces additional challenges. For future studies, we recommend a study protocol which considers these challenges. A combination of *in vivo*, *ex vivo* OCT imaging and histological analysis of the same tissue sample can be helpful. However, one should consider that normal tissues cannot be resected for study.

LIMITATIONS OF THE SINGLE SCATTERING MODEL

The single scattering model assumes that the detected backscattered light has interacted with the sample in a single scattering event. However, in highly forward scattering tissues, multiply scattered light contributes significantly to the OCT signal. Multiple scattering decreases the value of experimentally extracted μ_{OCT} compared to the sample's μ_S and degrades the axial resolution of the OCT image.[4,5] The probability of multiply scattered light contributing to the OCT signal increases for strongly scattering and forward scattering samples, in systems with low numerical apertures and at larger depths. Two approaches including multiple scattering in the description of the OCT signal are proposed in literature: Monte Carlo simulations and the extended-Huygens Fresnel (EHF) model. Monte Carlo simulations are based on probabilistic photon tracing simulations for which the outcome depends strongly on the chosen input parameters such as systems numerical aperture and the phase function of the sample.[6] The EHF model is an analytical model describing light propagation through homogeneous turbid media, valid for scattering anisotropy values above 0.7, which corresponds to particle diameters above 1 μm for the calculations shown in Figure 1. The strength of the EHF model is that the variation of any parameter in the model can be changed easily to study its influence on the retrieved optical properties.[2,5] In this thesis we have adopted the EHF model to estimate the contribution of multiple scattering (chapter 3). However, because of competing parameters in the EHF model, a priori input of sample properties was needed for the simulations and estimation of multiple scattering.[7] From the obtained model-based simulations we conclude that, for the experimental settings and samples under study, the experimentally obtained μ_{OCT} starts to deviate more than 10% from the sample's μ_S for samples with an anisotropy value g > 0.8 or a scattering coefficient μ_S > 10 mm^{-1}. In these cases, multiple scattering should be considered in order to accurately map μ_{OCT} to μ_S. It should be noted that the contribution of multiple scattering depends on both sample parameters and the systems' numeric aperture, therefore the results discussed in this thesis, measured at a numeric aperture of 0.02, are expected to differ for other numerical apertures.[8]

A crucial assumption in the determination of μ_{OCT} is the homogeneity of the sample over the A-scan depth range used to estimate μ_{OCT}. Many biological tissues possess a layered structure and are heterogeneous. The ROI is preferably chosen such that the obtained μ_{OCT} is obtained from a homogenous region. The capacity to find such a region is highly dependent on the specific tissue, and depends on the contrast between tissue layers and structures. Preprocessing of the data, by lateral averaging, contrast enhancement and segmentation of tissue layers can be helpful. Furthermore pixel-based methods to extract μ_{OCT} from OCT images can be used to account for axial heterogeneity.[9] Additionally, it is shown that the OCT speckle distribution relates to the organization of the scattering particles[10], and therefore might be a good indication of tissue homogeneity, which then can be used to select ROI's for μ_{OCT} analysis.

CALCULATION OF SCATTERING PROPERTIES: FROM DISCRETE RANDOM MEDIA TO TISSUE

Scattering properties of spherical particles can be calculated using Mie solutions to the Maxwell's equations, referred to as Mie theory. For accurate calculation of concentration-dependent scattering properties of non-dilute particle concentrations (>2 volume %), Mie calculations can be augmented by the Percus-Yevick structure factor, to include particle organization in the description of scattering behavior. We propose to account for the effect of dependent scattering by using the Percus-Yevick structure factor combined with Mie theory.[8,11] The influence of the Percus-Yevick structure factor on the optical properties and phase function are illustrated in appendix VII and VIII, respectively.

The theoretical framework presented in the first part of this thesis describes the OCT signal for discrete random media (DRM). Likely, the scattering properties of tissue are more realistically described using a Continuous Random Medium (CRM) formalism.[12] However, the parameters for CRM modeling (refractive index correlation length, refractive index variance, 'fractal parameter') are not easy to control in samples made for validation. We start with DRM because the samples can be controlled and well characterized. Moreover, the optical properties of DRM can be obtained by straightforward calculations using Mie theory together with the Percus-Yevick structure factor. By comparing theoretical predictions with experimental results we are able to validate this approach.[8] As a next step we propose to move to polydisperse samples. For bi-disperse samples, analytical solutions may still be available allowing thorough validation. Samples with a broad distribution of spherical particles, such as Intralipid, form an interesting case since it may be possible to describe them both by formalisms based on (polydisperse) DRM and based on CRM. Our expectation is that, ultimately, this will yield a better physical interpretation of CRM-derived properties.

FUTURE RESEARCH

In conclusion, quantitative OCT is especially useful as a tool for the detection of abnormalities in surrounding normal tissue, which can be used for optically guided biopsy. Furthermore, the non-invasive imaging capability of OCT enables measurement of the same location without disturbing the tissue under study, permitting the observation of dynamic processes at the same location.

In future research simulations of OCT data[6,13–16] can be used to predict the expected OCT image and quantitative OCT parameters. The theoretical framework presented in this thesis allows for prediction of such parameters for DRM. Monte Carlo based simula-
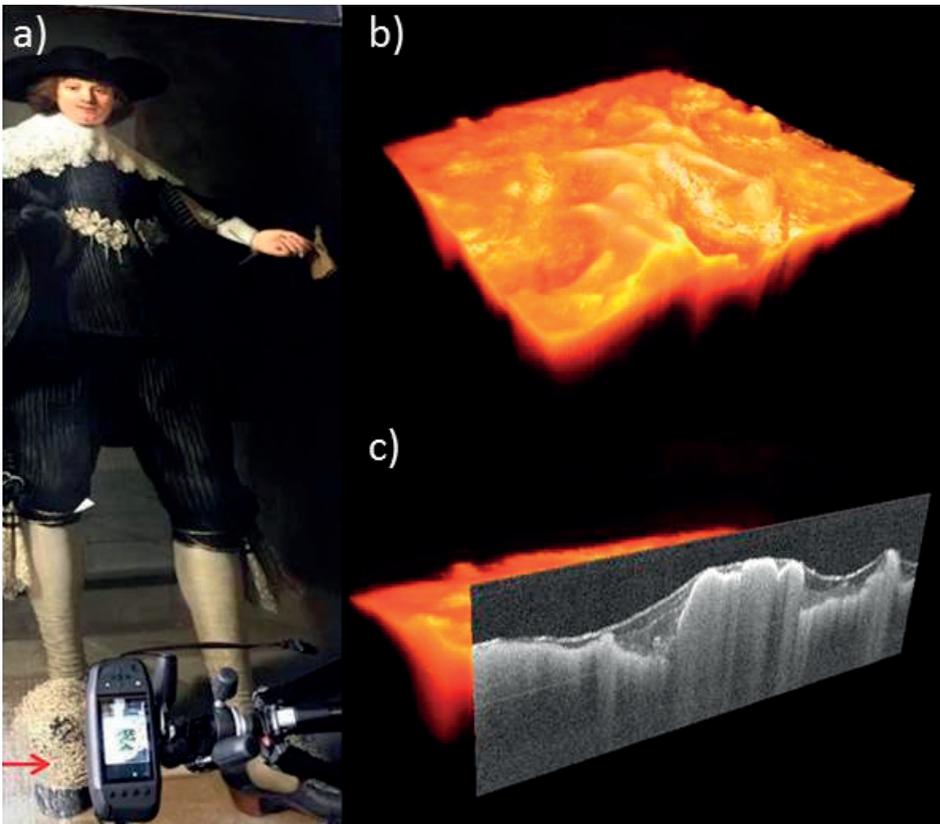

Figure 2. 3D OCT images of Rembrandt van Rijn, Portrait of Marten Soolmans (1613-1641), 1634, oil on canvas, h 207,5 x w 132 cm, inv. no. SK-A-5033, joint acquisition by the Dutch State and the French Republic, collection Rijksmuseum/collection Musée du Louvre. a) Detail of the rosette of his right shoe before restoration. b) a volumetric image c) a cross sectional image which shows layers of paint and varnish. The OCT image was collected using a swept source OCT system with a center wavelength of 1060 nm, from an area of 5 by 5 mm.

tion[6,13,14] can be applied to estimate quantitative OCT parameters, although the results of the simulations strongly depend on the input of the optical geometry and assumed phase function. Munro et al.[16,17] demonstrate a 3D mathematical model of OCT image formation, based on Maxwell's equations. Such sophisticated algorithms are a promising tool, however the structural and optical properties of the sample are needed as an input for the calculations, which is challenging for biological tissue. Information on the structural and optical properties of biological tissue may potentially be obtained using other probing modalities. Knowledge on cellular changes at different stages of disease can be used to create a library. Combined with understanding how these cellular changes influence tissue optical properties, the OCT signal and quantitative parameters can be simulated beforehand in order to design the experimental protocol accordingly.

Besides clinical applications, which are the main focus of this thesis, quantitative OCT could also be a useful tool in material and cultural heritage science[18,19]: Figure 2 shows a cross-sectional image of a small area on a Rembrandt painting measured during restoration of the painting at the Rijksmuseum Amsterdam. These measurements demonstrate the feasibility of non-contact high-resolution imaging of oil paintings using OCT. Furthermore, calculation of scattering properties using the theoretical framework presented in this thesis may be beneficial in other research fields investigating samples of relatively simple and known composition. Combining such calculations with quantitative analysis of OCT data could therefore be a powerful tool in research fields requiring non-contact (time-resolved) material analysis

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