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Optical coherence tomography for coronary artery disease : analysis and applications

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SUMMARY AND DISCUSSION

7.1 Summary

The aim of this thesis was to develop a software pipeline for tissue analysis in IVOCT by systematically addressing different open questions for analysis. The absolute intensities of comparable tissue regions in IVOCT images were speculated to be affected by the position of the catheter due to a difference in light loss caused by two factors, the traveling distance in the flush medium and the incident angle of light entering the arterial wall. This has been inferred mainly based on empirical evidence in combination with specialized tissue optics knowledge [34] and the studies of other catheter based imaging modalities such as IVUS. In Chapter 2, we report on a first attempt to quantify the correlation between the position of the catheter with respect to the luminal wall and the image intensities. Statistical analysis based on a hierarchical linear model showed that both factors affect image intensities within a superficial tissue layer significantly with $p < 0.001$, as either aspect increases, the intensity tends to decrease. A potential compensation was suggested and application experiments shown its potential for enhancing the visualization and BVS struts detection with the signal levels being balanced circumferentially. Visual assessment showed that attenuated structures were enhanced when the catheter was eccentric and the blood was poorly flushed. BVS detection for 6 out of 8 pullbacks was improved by 1 to 6.6 percent in F -score. On the other hand, the generalization of the algorithm was limited due to the fact that it is using an estimated intercept which is pullback-dependent.

Since the attenuation coefficient represents the decreasing trend of signals without involving an intercept term, it is less dependent on the catheter position and other related parameters. In the remaining work, our attention is focused on the estimation of this optical property. Until recently, region-based curve-fitting approaches have been predominantly used for attenuation calculation. As a pixel-based estimation, using the Depth-Resolved (DR) model has the advantage of being less dependent on local homogeneity and preserving original resolution. We implemented the DR-model for IVOCT images in Chapter 3. In addition to the attenuation coefficient, we further extended the model to estimate a backscatter term, and proposed an algorithm to exclude the noisy region at the end of the A-lines. For the first time, it was implemented in IVOCT images with fast and robust calculations. We analyzed the attenuation

coefficient, backscatter term and the image intensity in regions of interest (ROIs), which were delineated referring to corresponding histopathology. The optical values in the ROIs were reported and their distributions were further compared with 2-sample t-test to evaluate the potential for distinguishing six types of tissues. Results show that the IVOCT intensity, DR attenuation coefficient and backscatter term extracted with the reported implementation are complementary to each other in characterizing six tissue types: mixed, calcification, fibrous, lipid-rich, macrophages and necrotic core.

During the implementation of the DR model, we encountered unstandardized intensity ranges which resulted in different estimations even with the same approach. This is because different vendors follow different ways to store the data, which are unknown. Since 16-bit data yields values in comparable range with the published numbers, we applied a looked-up table to convert the 8-bit Terumo data into a 16-bit St. Jude like range for calculation in Chapter 3. This approach has been later improved using an exact histogram specification technique presented in Chapter 4. IVOCT pullbacks were matched according to visual landmarks, and the matching error was analyzed at both histogram and local intensity level. Two schemes, one global one local, for the determination of target histogram were compared. The leave-one-out validation shows that dissimilarities between the two pullbacks matched by the two schemes are comparable across the entire validation data set. Despite the errors caused by empirical matching, catheter position and histogram-based technique, the total matching difference was shown to be relative small. For the first time, this issue has been addressed with purely *in vivo* images rather than experimental data acquired with physical laboratory settings. The proposed matching framework can be further adopted for the intensity standardization across other OCT systems or other multi-slice imaging modalities where the intensity's order is maintained.

For the application of the DR algorithm, the optical parameters were analyzed as features for the maturity of post-stenting neointima in Chapter 5. The three factors DR attenuation, backscatter term and image intensity were determined in the neointima of both superficial and deep layers with fixed thickness. Comparison of the neointima in BVS struts with that in CoCr-EES strut showed a lower attenuation coefficient in both the superficial and the deep layer. The backscatter term and image intensity term in superficial neointima were comparable in the superficial layer but lower in the deep neointima. In general, the maturation was comparable while the change of lipid content in neointima was less prominent in BVS strut stents.

For the differentiation between thrombus types analyzed in Chapter 6, the three values were analyzed within consensus delineated regions of thrombi. Results showed two types of thrombi can be well differentiated using regional statistical values with high area under curve values. The determination is highly reproducible, less objective with minimum user-dependency. This warrants further investigation in larger randomized trials.

7.2 Discussion

The image intensity, the estimated attenuation coefficient and the backscatter term were considered in each study throughout the thesis. We have observed certain complimentary contributions of these three factors when comparing regional statistical analysis in Chapter 3. Meanwhile, we observed that the backscatter term tends to balance the intensity level circumferentially along the lumen, but how it adds to tissue characterization is yet not clear. Although the backscatter term is strongly related to the attenuation term by design, results show that it gives additional information for the differentiation of tissue types. Therefore, all three features are recommended to be calculated in studies such that they can be analyzed in meta-analysis in the future. Among these three parameters, the influence of estimated attenuation is most distinguishable and perceivable. From an image processing viewpoint, the estimation of DR attenuation can also be considered as normalization of intensities at a certain pixel position with the summation of intensities behind it. Structures can be enhanced when shadows occur due to high attenuation or reflection. Therefore, the estimated attenuation coefficient can potentially enhance the detection of structures including superficial dense macrophage infiltrations, TCFAs, red thrombi and metal stents.

Indication of macrophage infiltration: In Chapter 3, the carpet view of attenuation coefficient (Fig. 13) shows groups of regions of high values with dark shadows (Fig. 15). Their histology counterparts at four sites indicate that these regions may be associated with dense macrophage infiltrations and warrant further research. As it has been discussed in the work from Phipps et al. [61], that there are two types of macrophages; M1 macrophages that engulf lipid particles and form the necrotic core while M2 macrophage are more densely constructed with high reflection and serves for anti-inflammatory purposes. They also argued that only those macrophages that engulf lipid particles cause dark shadows. The analyzed superficial macrophages in Chapter 3 present both dark shadows and much higher attenuation coefficient than any other tissue types. That may suggest the presence of both types of macrophages: the carpet view of attenuation coefficients can be a promising auxiliary tool to validate the aforementioned subtype macrophages.

Detection of IVOCT-TCFAs: Acute coronary syndromes (ACSs) have been confirmed to be highly associated with TCFAs, which is defined in histology anatomy as a thin fibrous cap ($<65\mu\text{m}$) on top of a large lipid pool. In IVOCT it appears as a signal rich layer followed by a signal poor region separated with a diffused border in between. In the meanwhile, some other structures can be misread as TCFAs [8], such as the tangential signal dropout artifact, dramatic signal loss due to intraluminal thrombus and residual blood, or the aforementioned superficial macrophage infiltration. We refer to all structures looking like TCFA in IVOCT image as IVOCT-TCFAs. The detection of IVOCT-TCFAs should be considered as

a next step. The largest obstacle is the generalization of ground truth. The quality of IVOCT is restricted by its high noise level, and requirement of flushing and operator expertise. TCFA classifiers require large scale of training and validation *in vivo* data. It is highly challenging to acquire corresponding histological confirmation for ground truth. Therefore, the ground-truth generated in IVOCT images can be disturbed by the aforementioned artifacts. A suggestion is to generate a ground truth of IVOCT-TCFAs. The catheter position, attenuation of residuals in the lumen, and the attenuation of the cap can be analyzed as post-processing to refine the detection. The cap thickness should be measured with validated algorithm and reported as an important population property.

Detection of IVOCT thrombus: Encouraged by outcome of the work in Chapter 6, automated thrombus detection may be helpful for both further validation with larger data sets and clinical application in the future. In CAD patients, thrombi are associated with the erosion or rupture of the endothelium. To determine the backside border of a red thrombus, the algorithm proposed in Chapter 3 should be used. A challenge for thrombus detection can be the lumen border detection for embolic white thrombus and red thrombus of moderate size. In the former case, the lumen border can be difficult to distinguish due to the fact that the circumferential thrombus is closely attached to lumen border. In the latter case, the lumen border is invisible due to the high light loss. Both cases can cause an abrupt decrease of lumen radius in the longitudinal view of a pullback. Therefore, the continuity of lumen size in longitudinal view can be used as auxiliary information for lumen border determination. Thrombi detection and classification can also contribute to a detailed evaluation of iatrogenic damage during PCI and a better therapeutic treatment.

From the viewpoint of feature analysis, results indicate that the proposed pipeline can enhance the differentiation of tissue types using traditional machine learning classification. Traditional classifiers meet an upper boundary of performance once the size of training data is above a certain scale, while the prediction accuracy of a deep learning network can approximate to one as the size of training data continues to grow [150]. An interesting question is whether the estimated optical terms can benefit the detection of deep learning classifiers. However, this requires well-labeled training data, which is a well-known bottleneck in introducing deep nets to new imaging modalities such as IVOCT. Using the proposed pipeline as a preprocessing step can reduce the irrelevant variations for tissue recognition. In the meanwhile, the calculation of local DR attenuation involves the regularization of summation intensities behind a specific pixel position, thus the estimated value is location dependent. This type of information usually cannot effectively be learned even by deep networks. Therefore, using the proposed pipeline as preprocessing is expected to speed up the training convergence and increase the prediction accuracy for the same amount of data.

7.3 Future work

This work aimed to look into tissue recognition based on image data. We aimed to develop an analysis pipeline that can be ultimately used directly with data acquired in the catheterization laboratory without additional measurements. We extensively analyzed the variation range of measured values that can be caused by catheter dependent parameters such as focal point and incident angle. However, we did not include solid experimental control groups for concrete accuracy analysis. The validation of estimated attenuation coefficient and backscatter terms with phantom data can be found in the literature [59, 64]. For the intensity standardization framework, validation with data acquired from phantoms or ophthalmology data can be interesting for the future work since it allows for more control of the image alignment. However, it remains challenging to analyze the matching effect caused by the difference in catheter position, the pressure and strain on the vessel wall during cardiac cycle, etc. The effect can be monitored using high-speed OCT and electrocardiography (ECG) gating. Currently developed systems can acquire 100-mm-vessel within one second [151], which allows for imaging a long coronary segment within one cardiac cycle. Acquiring images at the same cardiac phase can minimize the cardiac motion differences. Another interesting attempt can be, if technically possible, building an inter-vendor system to combine catheters from two vendors as one such that images can be acquired at the same time, thus the concern over image alignment can be avoided.

As the algorithms for deep learning are becoming more efficient, it may hold promise for IVOCT image analysis in the future. A general structure can be constructed for stent struts detection to tackle the broad range of designs of stent. Using deep learning for intensity standardization can hopefully contend with the local variation better with higher performance than the proposed histogram-based technique, and it requires no maintained intensity order. A generative adversarial network would allow for the generation of artificial images. This is even more promising when combined with multimodal imaging. IVOCT has the shortcoming of limited imaging depth, thus it cannot offer information of plaque size and vessel remodeling. This information can be augmented by IVUS. Combining IVOCT with IVUS would preserve the advantages of both modalities at the expense of imaging speed. More existing techniques include near-infrared reflection spectroscopy (NIRS), near-infrared fluorescence (NIRF), and fluorescence lifetime imaging (FLIm) [16]. Since these techniques do not provide depth information, these techniques have been combined with IVUS or OCT catheters to offer direct information of tissue compositions per A-line. The intravascular photoacoustic (IVPA) imaging detects similar tissue components as those aforementioned techniques but with structural information at resolution of IVUS. Multimodal imaging allows for perfect inter-modality matching. Since images are acquired simultaneously, it allows for performing data alignment regardless the cardiac cycle. Once they are well validated, it is expected that the acquired images can evolve into *in vivo* alternatives for histological data for generating large random ground-truth

for training tissue classifiers. Given an image from one modality, it is then possible to predict its counterparts from other modalities. This can be further used to perfect the functionality of IVOCT and also possible to speed up the validation work of new techniques in the future.