Chapter 10

Summary and conclusions

10.1 Summary

In this thesis we developed and evaluated several methods for the automated analysis of the carotid artery vessel wall using multi-sequence MR vessel wall images to assess atherosclerosis. **Chapter 1** provides a general introduction into atherosclerosis and different stages of the disease were described including the importance to differentiate between stable and vulnerable plaques. Several non-invasive imaging techniques were discussed and the advantages of multi-sequence MRI were highlighted. A standard workflow for the manual analysis of these images was presented and existing methods for the automated analysis of these images were discussed.

A new method to segment the vessel wall boundaries was presented in **chapter 2**. The segmentation method uses a 3D deformable vessel model requiring only minimal user interaction by combining 3D MRA and 2D vessel wall images. Comparison of the automated method with manual segmentation showed substantial agreement with slight underestimation and a proportional error of the vessel wall thickness and volume. However, the automated method demonstrated improved interobserver agreement, improved inter-scan reproducibility and was substantially faster. Advantages over existing methods were that the method uses a true 3D model, which can be applied to both isotropic and non-isotropic image data, instead of segmenting the vessel wall boundaries in each image slice independently, as was done in other methods. This property is especially helpful in areas where the edges of the vessel wall are vague or poorly defined as in the bifurcation area. In case of a vague or missing edge in an image slice, edge information from neighboring slices is taken into account to guide the model to the correct location. The same effect applies to the bifurcation area, where most segmentation methods have the tendency to expand into the ECA, but this effect is limited for the 3D vessel model as edge information from neighbouring image slices is used during the model fitting.

In **chapter 3**, the underestimation of the 3D deformable vessel model segmentation method was addressed by adding a postprocessing step in which systematic segmentation errors were corrected by using a learning-based vessel segmentation correction method. This method can correct systematic errors caused by differences in image characteristics when using different MR acquisition parameter settings or different scanning equipment, and can correct for the limited flexibility of the 3D segmentation model. The application of the learning-based vessel segmentation correction method showed a small improve-

ment for the segmentation of the lumen boundary and a major improvement for the outer wall. After adding the learning-based segmentation correction step, the segmentation results were comparable to the manual annotations in terms of vessel wall dimensions and can therefore be used to replace the manual measurements speeding up the current analysis. Additionally, this development opens up possibilities for population studies with a large number of subjects where manual measurements becomes infeasible. Moreover, the learning-based segmentation correction method is potentially a powerful tool which can be applied to other automated segmentation problems. It can be used to adapt an automated segmentation result to an observer (e.g. the observer draws the contours on the rise of the edge, while the automated method searches for the strongest edge), or to adapt an existing method to different images.

The main theme of **chapters 4 and 5** is image registration, the automated alignment, of the multi-sequence MR images within one scan session and between scan sessions. In **chapter 4**, the need for image registration was shown by quantification of patient motion during one scan session. This quantification showed that the average misalignment is considerable and that patient movement occurs in all three dimensions. Different automated image registration experiments were performed in which several carefully selected, critical components of the registration procedure were optimized and quantitatively validated on a large group of patients. The optimal registration strategy was faster than manual alignment by a human expert, and provided similar accuracy. The results showed that automated image registration can replace the manual alignment procedure. This is the first study in which patient motion was quantified, a 3D deformable transformation model was used, and the registration experiments were validated on a large set of patient studies using quantitative measures. Additionally, the optimal registration strategy was validated on a more recent 3.0T dataset. The results of the 3.0T dataset were in line with the results of the 1.5T dataset showing that the same registration strategy can be applied to newer MRI data.

In **chapter 5** image registration is used to improve the comparison of baseline and follow-up images in serial MRI studies. Traditionally, observers either visually match each image slice of the baseline study with an image slice of the follow-up study and compare area measurements of the vessel wall and plaque components, or do not perform any matching and compare volume metrics based on the whole vessel. In both cases, only a small part of the available image information is used in the analysis. In our approach, 3D image registration was used to obtain point correspondence between images from different timepoints. Using this correspondence, measurements in the baseline study can be related to measurements in the follow-up study in high detail. Additionally, 3D visualization techniques were applied to present local changes in vessel wall morphology using difference maps which were color-coded on a mesh of the lumen segmentation of the baseline image. This approach is an improvement over the traditional volume-based image comparison and provides a detailed view of local differences over time improving insight into the disease progression of an individual patient.

In **chapters 6 to 9** pattern recognition techniques were applied for the analysis of atherosclerotic plaque components in MR vessel wall images. In **Chapter 6**, a study was presented in which an automated segmentation method was used to classify plaque components based on in vivo MRI from a multicenter study. The automated segmentation method employed a supervised classifier which was trained using intensity and gradient information from the MR sequences and morphological information such as local vessel wall thickness. The results indicated that it was possible to automatically detect carotid

plaque components with substantial or good agreement with visual identification, and that the volumes obtained manually and automatically were reasonably consistent for hemorrhage and lipids but not for calcium. The current results show that automated segmentation in a multicenter study is feasible provided MR protocols and acquisition parameters are standardized between centers. The results are promising, but improvements are still needed as the agreement between automated and manual segmentation was reasonable. The current results can serve as an initial segmentation to speed up the manual segmentation procedure.

In **chapter 7** the effect of 3D morphological features, image normalization strategies and composition of the training set on the accuracy and reproducibility of supervised plaque classification was investigated. Image normalization is often performed using the median signal intensity value of a 4x4 cm^2 square region of interest around the lumen, which is a surrogate measure for the signal intensity of the sternocleidomastoid muscle which is used as reference during manual segmentation of plaque components. Our results showed that a normalization approach using intensity scaling provided better results than the region of interest based approach. Interestingly, our results also showed a low agreement between the median value of the 4x4 cm^2 region of interest and the median value of the sternocleidomastoid muscle. The agreement between manual and automated segmentation was significantly improved by using the 3D distance to the flow divider feature, normalization based on intensity scaling and a training set based on the intersection of two repeated reads. Finally, the results showed that automated segmentation is more reproducible than manual segmentation.

In **chapter 8** pattern recognition techniques were applied to investigate the added value of two MR sequences at high field, inversion recovery spin echo and T1 weighted gradient echo with fat suppression, for identification of unstable plaque components. Instead of using the Euclidean distance measure, the Mahalanobis distance measure was used to quantify contrast between plaque components in MR sequences. The Mahalanobis distance measure is scale-invariant and takes into account the covariance between the samples, enabling comparison of image contrast between different MR sequences which is not possible while using the Euclidean distance measure. As a proof of concept, two automated segmentation experiments were performed using an Euclidean distance classifier and a Mahalanobis distance classifier. The experiments showed a better performance for the Mahalanobis classifier.

Chapter 9 presents another application of pattern recognition techniques for multi-sequence vessel wall imaging. In this chapter, automated segmentation was used to objectively evaluate an MR sequence protocol for the detection of soft plaque in the carotid artery. The approach allows development and optimization of an MR imaging protocol by investigating the tradeoff between scan duration and automated segmentation performance possibly leading to shorter scanning times and better image interpretation. This approach can be easily generalized and can therefore potentially be applied to other research fields focusing on different diseases and anatomical regions.

10.2 Conclusion

The main goal of this thesis was to develop methods for automated segmentation, registration and classification of the carotid artery vessel wall and plaque components using multi-sequence MR vessel wall images.

Several novel automated image segmentation and registration techniques have been developed. For each technique, existing methods were discussed to identify the need for developing a new method. Subsequently, the results of the new method were compared to existing methods where possible. All techniques were developed and validated using relevant patient data and reference standards. Manual segmentations created by experienced observers were used as reference standard and were in some cases based on histology data. At the end of each chapter, clinical implications were discussed by answering questions such as; what is the required user interaction to initialize the segmentation method?, how do the results compare to manual segmentation?, what is the decrease in analysis time?, and how does the technique fit into the current clinical research workflow?

To conclude, novel automated methods were developed which contributed to each step in the analysis of multi-contrast MR vessel wall images. Therefore, the main goal of this thesis has been realized.

10.3 Future directions

The work presented in this thesis is an important contribution to the automated analysis of multi-sequence MR vessel wall imaging of the carotid artery. However, given the current methodology, fully automated image analysis is not yet feasible, therefore motivating future research. Several possibilities exist to expand the current work: 1) The automated segmentation of the vessel wall boundaries is currently performed based on edge information of one contrast weighting. This method can be extended to include edge information from multiple contrast weightings possibly improving segmentation performance. 2) The 3D vessel model should be extended towards a full 3D bifurcation model to obtain a comprehensive description of this important region without having to correct for errors caused by the external carotid artery. 3) Another challenge is the automated segmentation of plaque components. The segmentation results are highly dependent on the choice of MR sequences and the quality of the acquired images. As these two factors are often difficult to control, a semi-automated approach should be investigated which speeds up the analysis time while preserving the segmentation performance of the observer. Additionally, the latest developments in T1, T2 and T2* mapping techniques should be closely monitored. These techniques allow the measurement of absolute T1, T2 and T2* relaxation times which are tissue specific biophysical MR properties. The quantitative properties, as opposed to working with relative signal intensities, promise a major contribution to automated classification of plaque components. 4) Develop a new workflow which is not analogue to the manual segmentation workflow. This might result in a different ordering of the segmentation steps or in hybrid approaches. Potential examples of hybrid approaches are the simultaneous segmentation of the vessel wall boundaries and registration of the multi-contrast images, and the simultaneous detection of the vessel wall boundaries and plaque components.

The availability of “good” datasets is currently limited. A good dataset should include a large number of MRI scans, preferably over 50, with sufficient image quality. Ideally, histology should be obtained and used as gold standard to assist the manual segmentation process. Alternatively, in case no histology is available, the image data should be analyzed by multiple trained observers who score the data individually and also perform a consensus reading. Acquiring such a dataset takes time as patients have to be recruited, scanned, and all data needs to be manually segmented. It would be helpful to the community to cre-

ate such as dataset and make it available to other research groups. A possible vehicle to do so is to organize a "challenge". A challenge allows different research groups to develop and test algorithms on a standardized set of data using a common evaluation framework.

A future direction on a higher level is to focus on treating the image data as a 3D volume instead of processing each image slice independently. As thinner image slices and isotropic datasets are becoming more popular, 2D segmentation methods will become computationally more intensive and can only take advantage of image information within the slice. Moreover, the analysis of patient movement and the automated registration results from chapter 4 showed the importance of a 3D approach. In the process of developing 3D segmentation methods, one has to be vigilant as a typical vessel wall imaging dataset is highly anisotropic and extensive use of interpolation can degrade the reliability of the results. Finally, as isotropic datasets are becoming more popular, manual segmentation becomes impractical, motivating the need for automated 3D segmentation methods.

Researchers developing image processing methods should work in close collaboration with MR pulse sequence developers and the clinicians who perform the MRI scanning. Various parameters, such as design choices in the MR pulse development, choice of applied MR sequences, setup of the scan protocol and slice planning, can have a substantial impact on the manual or automated analysis result of the image data. For example, an MR pulse sequence developer can focus on increasing the in-plane image resolution, which has a positive impact on the manual segmentation result, or put his effort into decreasing the slice thickness, which is more favorable from an image processing point of view. A good collaboration between the different parties will greatly contribute to a good end result.

Finally, the importance of a good software tool, which supports both the manual segmentation and automated analysis including correction of intermediate results, should not be underestimated. A good tool allows clinicians to efficiently view the image data and perform manual segmentations. These segmentations can then be used for the development and validation of new segmentation methods, which, in turn, can be added to the software tool to support the clinician. And, although the ultimate goal is to develop fully automated segmentation methods, results of newly developed segmentation methods will always need thorough visual verification and ideally limited manual corrections.