Carotid Artery Geometry and Plaque Quantification in CTA and MRI

Hui Tang
Carotid Artery Geometry and Plaque Quantification in CTA and MRI
INVITATION
To attend the public defense of my thesis
entitled

Carotid Artery Geometry and Plaque Quantification
in CTA and MRI

on November 27th 2013 at 12:30
in Senaatszaal room in Aula Congress Centrum of TU Delft

Before the defense, I will give an introduction on my research at 12:00

The ceremony will be followed by a reception

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Paranympths
Arna van Engelen
Reinhard Hameeteman
Stellingen

Behorende bij het proefschrift

Carotid Artery Geometry and Plaque Quantification

Hui Tang
November 27, 2013

1. Het combineren van informatie uit verschillende beeldmodaliteiten vergroot de robustheid van vaatas-extractie, terwijl de nauwkeurigheid afhankt van de modaliteit met de hoogste beeldkwaliteit. (dit proefschrift)

2. Plaque-weefsel kan geëxcludeerd worden van het gesegmenteerde lumen door gradiënt en intensiteitsinformatie te combineren. (dit proefschrift)

3. Automatische segmentatie van plaque bloedingen in T1-gewogen MRI geeft een betere inter-scan reproduceerbaarheid dan handmatige annotaties. (dit proefschrift)

4. Automatische kwantificatie van stenose in de halsslagader gebaseerd op CTA is nog niet voldoende nauwkeurig bij ernstige stenoses. (dit proefschrift)

5. Verbeteringen in algoritmes voor medische beeldanalyse zijn belangrijker voor klinische besluitvorming dan verbeteringen in medische beeldvormende technieken.

6. Het ontwikkelen van een gebruiksvriendelijke interface voor zelfontwikkelde software is efficiënter dan het trainen van een clinicus om de ontwikkelversie te gebruiken.

7. Het lezen van vakliteratuur is belangrijker voor een eerstejaars promovendus dan het schrijven van een artikel.

8. Motivatie is net zo belangrijk als talent voor het behalen van een doctorstitel.

9. In Nederland weerspiegelt de taal die gesproken wordt tijdens koffiepauzes het niveau van internationalisatie.

10. Het opvoeden van een baby helpt bij het begrijpen van leren zonder toezicht.

Carotid Artery Geometry and Plaque Quantification in CTA and MRI

Hui Tang
Carotid Artery Geometry and Plaque Quantification in CTA and MRI

Proefschrift

ter verkrijging van de graad van doctor
aan de Technische Universiteit Delft,
op gezag van de Rector Magnificus prof. ir. K.C.A.M. Luyben,
voorzitter van het College voor Promoties,
in het openbaar te verdedigen op woensdag 27 november 2013 om 12:30 uur
door

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The glasses image in the front cover is from BrettSelby.com
Summary

Carotid artery disease is one of the leading causes of death world-wide. Non-invasive imaging techniques play an increasingly important role in understanding and staging the preclinical and clinical stages of the disease, as they can be used to study characteristics of both the vessel lumen and wall. To facilitate standardized evaluations, these imaging data are ideally analyzed in a quantitative manner. Image-derived quantitative biomarkers of carotid artery disease have potential in prognosis, risk assessment and therapy planning. In this thesis, we present and evaluate automatic image analysis techniques for the extraction of quantitative imaging biomarkers related to carotid artery disease.

Carotid artery geometry is the first biomarker we study, as it may influence the progression of the disease. We develop and evaluate a semi-automatic method for carotid artery centerline extraction and lumen segmentation in multispectral MRI data and subsequently quantify carotid artery geometry from the centerline and lumen boundary. An iterative method is used that ensures that the centerline is not taking the inner curve, which is a common problem with centerline tracking approaches, but nicely approximates the medial axis of the carotids. We demonstrate that the carotid artery centerline can be extracted with an accuracy similar to the inter-observer variability and that the carotid lumen can be delineated with an accuracy close to the inter-observer variability. We also obtain good correlation between the biomarkers quantified from manual and automatic segmentation.

Carotid artery stenosis degree is the second biomarker we consider, as it is a generally accepted quantitative imaging biomarker in therapy planning of carotid artery disease. We present a method that segments the carotid artery lumen in CTA (computed tomography angiography). By incorporating intensity information and spatial information into a levelset evolution, the lumen can be segmented without including plaque tissue. We evaluate the method in a publicly available evaluation framework (challenge), where it ranks second among all submitted segmentation methods. We also develop an automatic method to quantify the carotid stenosis degree based on the automatically segmented lumen. Our results rank first among all submitted stenosis quantification methods. Additionally, we evaluate the semi-automatic CTA carotid stenosis quantification method on a large clinical data set. Next to stenotic degree, minimal
and reference diameter quantification as well as carotid artery detection are evaluated. The results indicate that although the method generally agrees well with observers in quantifying the minimal and reference diameter, there is limited agreement when categorizing severe stenoses.

Third, the presence and volume of intra-plaque hemorrhages is investigated, as it is an important risk factor for carotid artery disease progression. We present a method for intra-plaque hemorrhage segmentation in T1w-MRI, which requires neither manual nor automatic segmentation of the inner and outer vessel wall. We show that semi-automatic segmentation and quantification of intra-plaque hemorrhages is feasible with an accuracy in the range of the inter-observer variability. The method has good reproducibility with respect to rescanning and manual initialization.
Samenvatting

Aandoeningen aan de halsslagader (carotis) behoren wereldwijd tot de belangrijkste doodsoorzaken. Niet-invasieve beeldvormende technieken spelen een steeds grotere rol in het begrijpen en bepalen van de verschillende stadia van de ziekte, zowel voordat er klinische symptomen zijn als nadat er klinische verschijnselen zijn opgetreden. Deze beeldvormende technieken kunnen worden gebruikt om de eigenschappen van het lumen (het gedeelte waar het bloed doorheen stroomt) en de vaatwand van de carotis te bestuderen. Om de analyse van de carotis te standariseren is een kwantitatieve aanpak nodig. De op beeldinformatie gebaseerde kwantitatieve biomarkers van de carotis kunnen worden gebruikt in prognose, risicoanalyse en therapieplanning. In dit proefschrift presenteren en evalueren we verschillende automatische beeldanalysetechnieken voor de bepaling van kwantitatieve beeld-gebaseerde biomarkers van de carotis.

De geometrie van de carotis is de eerste kwantitatieve beeld-gebaseerde biomarker die we bestuderen, daar deze invloed kan hebben op het verloop van de ziekte. We ontwikkelen en evalueren een halfautomatische methode om de centrale as van het lumen in meervoudig spectrale MRI-data te bepalen en vervolgens de geometrie te kwantificeren aan de hand van de centrale as en de rand van het lumen. We introduceren een iteratieve methode om er zeker van te zijn dat we in gebieden waar het bloedvat een scherpe bocht maakt in het centrum van het bloedvat blijven en niet de bocht 'afsnijden'. Dit laatste is een veelvoorkomend probleem bij methodes om de centrale as van een bloedvat te bepalen. We laten zien dat de gepresenteerde methode voor de bepaling van de centrale as dezelfde nauwkeurigheid haalt als de variatie tussen twee waarnemers en dat de bepaling van de lumenrand een vergelijkbare nauwkeurigheid heeft. Daarnaast is er ook een goede correlatie tussen de gekwantificeerde geometrie op basis van de handmatig bepaalde lumenrand en die op basis van de gepresenteerde automatische methode.

De volgende biomarker die we onderzoeken is de stenosegraad van de carotis. Dit is een algemeen geaccepteerde kwantitatieve beeld-gebaseerde biomarker voor therapieplanning van aandoeningen aan dit bloedvat. We presenteren een methode die het lumen van de carotis segmenteert in beelden verkregen met tomografische angiografie (CTA). In deze segmentatiemethode maken we ge-
bruik van zowel intensiteits- als plaatsinformatie in de CTA-beelden. Op deze manier kunnen we het lumen onderscheiden van het aangrenzende plaqueweefsel. We hebben de methode met behulp van een vrij toegankelijk evaluatiesysteem (open competitie) gevalueerd en behaalden er de op n na beste positie in de ranglijst van alle gevalueerde lumensegmentatiemethoden mee. We ontwikkelden ook een methode om de stenosegraad te bepalen op basis van het automatisch gesegmenteerde lumen. Deze methode behaalde de eerste positie in de genoemde open competitie. In aanvulling op deze evaluatie hebben we de gepresenteerde halfautomatische CTA-stenosegraadmethode toegepast op een grote klinische dataset. Behalve de stenosegraad hebben we op deze dataset ook de bepaling van de minimale- en referentiediameter alsmede de segmentatie van het lumen van de carotis gevalueerd. Deze evaluatie laat zien dat, hoewel de resultaten van onze methode over het algemeen goed correspondeert met handmatige metingen van de diameters, de overeenkomst beperkt is als het gaat om het categoriseren van een ernstige stenosegraad.

Als derde hebben we de aanwezigheid en het volume van plaque-bloedingen onderzocht. Dit is een belangrijke risicofactor voor progressie van aandoeningen aan de carotis. We presenteren een methode om de plaats van deze bloedingen te bepalen in T1-gewogen MRI-beelden. Voor deze methode is het niet nodig eerst de rand van het lumen en de buitenwand van de carotis te bepalen. We laten zien dat halfautomatische kwantificatie van het volume van deze bloedingen mogelijk is met een nauwkeurigheid die in dezelfde orde van grootte ligt als de variatie tussen twee handmatige metingen. De methode heeft een goede reproduceerbaarheid met betrekking tot variaties in de handmatige initialisatie en het opnieuw scannen van de patiënt.
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Chapter 1

Introduction

1.1 Introduction

Carotid artery disease, the third leading cause of death in the world [77], is a disease caused by the build-up of fatty substances and cholesterol deposits, i.e. plaque, in the carotid vessel wall. In later stages of the disease, the buildup of plaque may narrow the internal or common carotid arteries, sometimes resulting in a decreased blood supply to the brain. The presence of carotid artery disease increases the risk of stroke. In eastern countries, for example China [43], carotid artery disease is a major cause of mortality and morbidity. The onset and progression of carotid artery disease often takes place without symptoms until a stroke or transient ischemic attack (TIA) [31] occurs. Early detection and assessment of the severity of carotid artery disease are of great importance to assist clinicians in selecting the proper treatment strategy, possibly preventing a clinical event [80]. Ultrasound, MRI and CT allow non-invasive visualization of the human carotid artery. They are increasingly used to image both the carotid artery lumen and wall. This permits researchers to investigate the progression of carotid artery disease, and relate features of carotid artery disease to clinical events. This knowledge will further aid clinicians in early detection of carotid artery disease and selecting the proper treatment plan.

Both research into the progression of carotid artery disease, and the use of non-invasive imaging of carotid artery disease in clinical practice, requires the extraction of relevant quantitative parameters (which we will refer to as "quantitative imaging biomarkers") related to carotid artery disease, such as stenosis grade, plaque volume and plaque composition. Manually extracting quantitative imaging biomarkers from imaging data is often a laborious procedure, prone to inter- and intra-observer variability. Therefore, there is a clear need for robust, accurate and reproducible automated image analysis techniques.
Chapter 1. Introduction

In this thesis, we describe techniques that we developed to semi-automatically, robustly and reproducibly segment carotid arteries and extract quantitative imaging biomarkers that are related to carotid artery disease. In the following sections, we briefly describe the anatomy and functioning of carotid arteries, introduce imaging techniques for visualizing carotid arteries and plaques, and discuss a number of imaging biomarkers that are relevant for detecting, treatment planning, and monitoring the progression or treatment effect of carotid artery disease. We then formulate the challenges and objectives of our research.

1.1.1 Carotid Artery

The carotid arteries are the blood vessels that supply oxygenated blood to the face, neck and brain. They are located on the left and right side of the neck. The right common carotid artery branches from the brachiocephalic artery ([www.wikipedia.org](http://www.wikipedia.org)) and extends to the right side of the neck. The left common carotid artery branches from the aorta and extends to the left side of the neck. Each carotid artery has three branches, see Fig. 1.1. Starting from the common branch, it splits into the internal and external branch near the top of the thyroid. The internal carotid artery supplies oxygenated blood to the brain and eyes. The external carotid artery supplies oxygenated blood to the throat, neck glands, tongue, face, mouth and ear.

![Figure 1.1: An illustration of the carotid artery anatomy, image from http://www.drugs.com/cg/carotid-artery-disease.html](http://www.drugs.com/cg/carotid-artery-disease.html)
1.1.2 The Atherosclerosis Disease

Atherosclerosis is a condition in which the arterial wall thickens as a result of the accumulation of fatty materials such as cholesterol [31]. It is a chronic inflammatory response in the arterial wall [70]. Atheromata are commonly referred to as atheromatous plaques. Mature plaques typically mainly consist of two components: soft, lipid-rich atheromatous and hard, collagen-rich sclerotic tissue. Fig. 1.2 shows the sclerotic component (fibrous tissue) which is usually by far the more voluminous component of a stenotic carotid plaque, on average accounting for more than 60% of its volume [92]. The soft tissues destabilize plaques, making them vulnerable to rupture, while the hard tissues tend to stabilize the plaque [31, 33]. Ruptures of the fibrous cap of the plaque, which is a layer that is composed of bundles of muscle cells, macrophages, foam cells, lymphocytes, collagen and elastin, may lead to the release of thrombogenic materials inducing thrombus formation in the lumen. The lumen could be fully occluded by the thrombus, which is called thromboembolism. Apart from thromboembolism, chronically expanding atherosclerotic lesions (stable ones) can also cause complete closure of the lumen. The chronically expanding lesions are often asymptomatic until lumen stenosis is so severe that oxygenated blood supply to downstream tissue(s) is insufficient resulting in ischemia.

1.1.3 Non-invasive Imaging Modalities for Carotid Arteries

In 1895, Wilhelm Conrad Rntgen discovered X-rays. After more than 100 years of contributions from physics, engineering, medicine, and computer science, we currently have imaging modalities that can visualize both human anatomy and function in 3D, ranging from the micro to the macro scale. Computed Tomography Angiography (CTA), Magnetic Resonance Imaging (MRI) and Duplex Ultrasound (DUS) are the three main imaging modalities specifically for carotid artery imaging. In the past Digital Subtraction Angiography (DSA) was used to assess the degree of stenosis and this technique is still considered to be the gold standard [6, 129]. Currently a non-invasive approach is used: DUS is usually performed as a screening modality to determine whether carotid artery stenosis is present [55] and CTA or MRA are subsequently performed to confirm the presence of stenosis and to assess more accurate the degree of stenosis [53, 83, 84, 128].

Computed Tomography (CT) reconstructs images based on the difference in the attenuation of X-rays by the various tissue types inside the human body [26, 44]. A typical CT scanner consists of an X-ray source and a detector that rotates around the subject, see Fig. 1.3. CT is an excellent imaging modality for high density structures such as bone and calcium, owing to the large differences
Figure 1.2: Illustration of atherosclerosis progression (With permission from Lippincott Williams and Wilkins/Wolters Kluwer Health: Molecular imaging of atherosclerosis for improving diagnostic and therapeutic development [89], copyright (2012))

in attenuation with surrounding tissues and air. To visualize the vasculature, which is less dense, a iodine-based contrast agent is injected into the lumen. This technique, CT angiography (CTA), can visualize the carotid artery lumen and can thus be used to assess lumen narrowing. Thanks to the introduction of multi-detector and multi-source CT, both the temporal and spatial resolution of CT imaging have increased tremendously over the last decade. With the most advanced scanners, a spatial resolution of around 0.5 mm can be achieved and slice thicknesses as thin as 0.3 mm [105]. At this spatial resolution, the calcium and lumen can be clearly visualized. An example of a typical CTA
1.1. Introduction

Figure 1.3: (a) Schematic design of CT image acquisition, (b) CT scanner, image source from http://mhealthinsight.com/2010/02/04/a-computer-tomography-exam-over-iphone-anyone/.

![CT Image Acquisition Schematic](image)

Figure 1.4: An example of CTA image for carotid artery

![CTA Image](image)

Image of the carotid artery is shown in Fig. 1.4. A disadvantage of CT/CTA is exposure to ionizing radiation. Even though recently much effort has been devoted to a significant reduction in patient dose [7], it still induces a (latent) cancer risk.

Magnetic Resonance Imaging (MRI) utilizes the principle of nuclear magnetic resonance (NMR) to image magnetic properties of atomic nuclei inside the body. An example of a MRI scanner is shown in Fig. 1.5. Even though the in-plane spatial resolution of MRI is usually lower than CT, one of the advantages of MRI over CT is that it does not use ionizing radiation. Another advantage is that MRI provides much better soft tissue contrast than CT. MRI is therefore an ideal imaging modality to visualize atherosclerotic plaque and distinguish the different plaque components. MRI can also be used to visualize the arterial lumen (MR angiography). The most widely used MR angiographic
imaging techniques are phase contrast MRI, time-of-flight MRI, and contrast-enhanced MRI. Phase contrast techniques yield contrast between flowing blood and stationary tissues by using velocity dependent changes in the phase of the magnetization. In time-of-flight MRA contrast is achieved from "fresh" blood flowing into a region of interest, where the stationary tissue signal has been saturated. In black Blood MRA the signal of blood is suppressed. Contrast-enhanced techniques use an intravenously injected contrast agent to selectively shorten the T1 of the blood [42]. Fig. 1.6 shows examples of the carotid lumen imaged with Black Blood MRA and Phase Contrast MRI.

1.1.4 Quantification of Carotid Atery Disease

The exact cause of atherosclerotic disease is unknown. Several conditions are risk factors for atherosclerosis, such as gender, advanced age, hypertension, smoking and diabetes [63]. The risk factors can be further divided into modificable and non-modifiable risk factors. Controlling modificable factors may delay the progression of atherosclerosis and hence reduce or prevent clinical events [63].

Many researchers have investigated the factors that affect plaque formation [21, 108, 8, 66]. Some of these factors are related to the carotid artery geometry. The carotid bifurcation angle, carotid tortuosity as well as the ratio between the cross-sectional areas in the common branch and internal branch have been associated with a higher risk for developing atherosclerosis [36].
1.1. Introduction

Figure 1.6: (a) Black Blood MRA image and (b) Phase Contrast MRI image of a carotid artery.

Lumen and plaque characteristics have been indicated as factors affecting plaque progression. Stenosis grade is an important clinical measure in deciding whether to perform a carotid endarterectomy, as it has been shown that for stenoses larger than 50%, a quick treatment is beneficial [129, 32, 6, 91]. However, vulnerability to rupture depends more on plaque composition - than on plaque size or degree of stenosis [81, 82]. A plaque with a lipid or necrotic core covered by a thin fibrous cap is associated with a high risk of rupture, while fibrous tissue and calcifications stabilize plaques [81, 82, 101, 86, 98]. As a result, both the degree of lumen narrowing and plaque composition are relevant measures to assess atherosclerosis severity, to predict plaque progression, and to guide therapy decisions.

To study the relation between risk factors, lumen characteristics and plaque characteristics on the hand, and plaque formation and plaque progression on the other hand, longitudinal studies including a large number of subjects are required. In such studies, extraction of imaging biomarkers via manual annotation is becoming prohibitive due to time constraints. Also, manual annotation is prone to inter- and intra-observer variability. Automated tools which are sufficiently accurate and reproducible are therefore highly desired. In addition, such automated tools would enable the translation of quantitative imaging biomarkers to clinical practice, to enable objective standardized measurements. In
this thesis, we therefore investigate automated methods to extract quantitative imaging biomarkers of atherosclerotic disease from CTA data. More specifically, we develop and evaluate methods to analyze the carotid artery lumen and intra-plaque hemorrhages, and apply these in the context of large clinical studies.

1.1.5 Lumen and Intra-plaque Hemorrhage Segmentation

There have been many papers on vessel segmentation. Recently Lesage et al. [67] provided a review of vessel lumen segmentation methods regardless of vessel types and imaging modalities. They classified methods with respect to the vessel models and vessel features that were used, and the method used in the vessel extraction step. For the carotid lumen segmentation methods, the carotid lumen is usually modeled as a 3D surface that represents a bifurcation [75, 97, 119, 120, 64, 52, 9]. Image intensity and gradient magnitude are two image features commonly used for carotid artery lumen segmentation. Extraction schemes such as Graph cuts [12], snakes [54], active shape/appearance model [24, 25, 23] and level sets [100] are currently the most popular ones. The level set and graph cut extraction schemes are usually initialized by either a manually or an (semi-) automatically extracted object skeleton.

Most of the published carotid lumen segmentation methods have been validated on a limited number of datasets [75, 97, 119, 134, 64, 52]. Some evaluations have been limited to one branch of the carotid artery [75, 120] or have been validated only for healthy vessels [97, 134, 64, 52]. Furthermore, except for the paper by Bijari at al. [9], all the existing method did not evaluate their ability on automatically quantifying the clinical relevant biomarkers from the segmentation, such as stenosis degree[75, 97, 119, 120, 64, 52, 9].

For the automated analysis of plaque components, such as fibrous tissue, lipids, or intra-plaque hemorrhage, pattern recognition and machine learning methods have been used [71, 47, 123, 122, 126]. The inner and outer vessel wall are commonly first delineated prior to plaque component classification. Subsequently, the plaque components are classified by a supervised classifier trained on a training set. Multiple features, such as normalized signal intensity, zero-, first-, and second-order derivatives at multiple scales, distance to the inner and outer wall as well as local vessel wall thickness have been used as features in the classification process. Currently, these methods are still laborious since the delineation of the inner and outer vessel wall is not yet fully automated [71, 47, 123, 122, 126].
1.2 This thesis

The sections above indicate that there is a clear need for extracting quantitative imaging biomarkers related to atherosclerotic vessel disease. Despite the efforts in this area, there are currently no accepted and validated automated tools available, which can be applied in the context of large clinical or population studies, or in clinical practice. This thesis therefore focuses on the development and evaluation of methods for the automated quantification of a number of imaging biomarkers for carotid artery disease in CTA and MRI, and their large scale application in clinical and population studies. The main contributions of the thesis are: 1) a method to segment the carotid artery lumen and to quantify the carotid geometry in multi-sequence MRI; 2) a method to segment carotid lumen for stenosis quantification in CTA; 3) a method to segment and quantify intra-plaque hemorrhage in MRI; 4) application of the CTA lumen segmentation and quantification method in a large longitudinal dataset.

Chapter 2 focuses on the automated segmentation of the carotid artery lumen from multi-sequence MRI data and the subsequent quantification of the carotid lumen geometry. We present a novel method for extracting the lumen centerline requiring only three mouse clicks for initialization. The subsequent carotid segmentation and geometry quantification process is fully automatic. The components of the method are (i) a novel iterative centerline extraction (ii) a level set based lumen segmentation approach, and (iii) a procedure to quantify the carotid artery geometry. The method is optimized in a training stage and the evaluation is carried out on a large dataset comprising 96 CTA scans.

Chapter 3 presents a method for carotid lumen segmentation and automatic stenosis quantification in CTA data. The lumen segmentation method presented in this chapter will not segment plaque components and voxels that surround the calcium. After successful segmentation of the whole carotid artery, the stenosis degree for the internal carotid artery is automatically determined. The whole procedure is evaluated on a publicly available multicenter database containing 56 CTA scans.

Chapter 4 presents a method for intra-plaque haemorrhage (IPH) segmentation and volume quantification in MRI. Currently, there is a large interest in the role of IPH in the stability of plaques. The method we present in this chapter does not require segmentation of the inner and outer vessel wall. Limited user interaction is required, making it suitable for intra-plaque segmentation in large studies. The method is optimized on 18 carotid arteries and quantitatively evaluated on 52 carotid arteries.

To further evaluate the segmentation and stenosis quantification method devel-
oped in Chapter 3, Chapter 5 applies the method on a dataset containing 404 carotid arteries from CTA imaging data collected in a prospective study. This chapter does only quantify the stenosis degree but also compares the automatic stenosis categorization and automatically extracted minimal and reference diameters to manual measurements.
Chapter 2

Lumen Segmentation for Carotid Geometry Quantification in Multispectral MRI

Quantitative information about the geometry of the carotid artery bifurcation is relevant for investigating the onset and progression of atherosclerotic disease. This chapter proposes an automatic approach for quantifying the carotid bifurcation angle, carotid area ratio, carotid bulb size and the vessel tortuosity from multispectral MRI. First, the internal and external carotid centerlines are determined by finding a minimum cost path between user-defined seed points where the local costs are based on medialness and intensity. The minimum cost path algorithm is iteratively applied after curved multi-planar reformatting to refine the centerline. Second, the carotid lumen is segmented using a topology preserving geodesic active contour which is initialized by the extracted centerlines and steered by the MR intensities. Third, the bifurcation angle and vessel tortuosity are automatically extracted from the segmented lumen. The methods for centerline tracking and lumen segmentation are evaluated by comparing their accuracy to the inter- and intra-observer variability on 48 datasets (96 carotid arteries) acquired as part of a longitudinal population study. The

This chapter is based on:
evaluation reveals that 94 of 96 carotid arteries are segmented successfully. The distance between the tracked centerlines and the reference standard (0.33 mm) is similar to the inter-observer variation (0.32 mm). The lumen segmentation accuracy (average DSC = 0.89, average mean absolute surface distance = 0.31 mm) is close to the inter-observer variation (average dice = 0.92, average mean surface distance = 0.23 mm). The correlation coefficient of manually and automatically derived bifurcation angle, carotid proximal area ratio, carotid proximal bulb size and vessel totuosity quantifications are close to the correlation of these measures between observers. This demonstrates that the automated method can be used for replacing manual centerline annotation and manual contour drawing for lumen segmentation in MRIs data prior to quantifying the carotid bifurcation geometry.
2.1 Introduction

Carotid atherosclerosis, i.e. plaque build-up in the arterial wall, is a major cause of mortality and morbidity [31]. A large number of research institutes have studied the factors affecting plaque formation and growth [21, 8, 108, 66]. Friedman et al. [36] suggested that certain individuals might be at higher risk of developing atherosclerosis owing to their particular vascular geometry. Several studies have investigated the potential role of vessel geometry in developing atherosclerosis [115, 107]. Thomas et al. [115] showed that variation in carotid bifurcation geometry significantly increases with age and early atherosclerotic disease progression. In a longitudinal study, Smedby et al. [107] showed that plaque progression was associated with a high mean value of vessel tortuosity in femoral arteries. Lee et al. [66] studied the relation between various geometry factors, such as carotid ratios and tortuosity, and disturbed flow. Whether carotid artery geometry is a factor in the onset and progression of atherosclerosis for individuals is still unclear and needs to be investigated in longitudinal studies. To support the analysis of imaging data acquired in such studies, a method for accurate, objective and robust carotid artery geometry quantification is required. Arotid MRI is a histologically validated method for visualizing atherosclerosis progression and regression [117]. The current work is being carried out in the context of a population study [45], where a series of MRI sequences including Proton Density Weighted Black Blood (BBMRI) and Phase Contrast MRA (PCMRA), two MR angiography techniques not requiring contrast agent, are used for carotid lumen and plaque visualization. The non-invasive nature is the main advantage of BBMRI and PCMRA over CTA and contrast enhanced MRA.

Several authors investigated carotid artery lumen segmentation in different imaging modalities [134, 64, 52, 1, 75, 9, 62], using explicit contours or surface deformation schemes such as snakes [54] and geodesic active contours [17]. There exist several ways to categorize lumen segmentation methods [67], in this chapter we discuss the deformable model based carotid lumen segmentation methods according to the type of image features used: gradient only [134, 64, 52, 1, 9] or a combination of intensity and gradient features [110, 75, 62].

In the first category, Yuan et al. [134] utilized a snake based approach to find the inner and outer vessel walls of carotid arteries in BBMRI and quantified the cross sectional area. This method required a quite accurate initialization comprising of a manually annotated contour for both the inner or the outer vessel walls. This method was evaluated on 5 subjects (10 carotid arteries). Since the initial contour should be carefully annotated, it requires considerable user interaction. Ladak et al. [64] adapted a 2D discrete dynamic contour
method to segment the carotid arteries. The method was initialized by selecting 5 points for each contour. To reduce segmentation errors, they allowed user interaction afterwards. Their work was evaluated on 12 images (3 images per carotid artery, 4 carotid arteries). Jin et al. [52] used a deformable model initialized by a manually obtained centerline to segment the whole carotid artery and evaluated their work on 5 subjects (10 carotid arteries). Bijari at al. [9] segmented carotid arteries in 122 Contrast-Enhanced MRA datasets using level set evolution.

In the second category, Tang et al. [110] segmented the whole carotid artery lumen in BBMRI using geodesic active contours initialized by a manually obtained centerline in 48 subjects (96 carotid arteries). This requires considerable user interaction. Similarly, albeit on CTA data, Manniesing et al. [75] steered a levelset evolution using both gradient and intensity features and evaluated the method on 204 carotid arteries. As part of a challenge for carotid lumen segmentation in multi-center CTA data [39], Krissian et al. [62] evolve the levelset using both intensity and gradient information in 41 carotid arteries.

In this chapter we present a method for carotid centerline extraction and lumen segmentation followed by quantification of the lumen geometry. The method is evaluated on 48 MRI datasets acquired in the context of a longitudinal population study [45]. In this study, owing to the population based settings, BBMRI and PCMRA were used rather than Contrast Enhanced MRA. BBMRI offers a better lumen representation than PCMRA and thus is well suited for lumen segmentation. Both the reference standard and the automatic segmentation are obtained from BBMRI. However, as PCMRA provides good background suppression, for a more automatic segmentation approach, it is useful to take into account information provided by PCMRA to improve the robustness of the centerline extraction. It helps to prevent the centerline tracking from running outside the carotid arteries or from switching between the internal (external) and external (internal) branches. We therefore present a method that uses both BBMRI and PCMRA to achieve a robust initial centerline with user interaction limited to the selection of three seed points. A centerline refinement step from the initial centerline is then made after curved multi-planar reformatting (CMPR) of the BBMRI image stacks. We subsequently use a topology-preserving geodesic active contour to segment the carotid artery. The topology-preserving levelset evolution is initialized by the centerlines and steered using intensity information. The segmentation method is evaluated quantitatively on 96 carotid arteries in 48 subjects. After segmentation, the bifurcation angle, the proximal bulb size, the proximal area ratio for the carotid artery, centerline tortuosity of automatically defined branches are quantified.

Our work has five contributions. First, we propose a semi-automated centerline extraction method in multispectral MRI to maximize extraction robustness.
2.2 Methods

Second, we propose an iterative centerline refinement procedure to obtain very accurate centerlines even in highly tortuous vessels. Third, we propose a method to segment the carotid lumen from BBMRI using local intensity information. Fourth, we demonstrate the accuracy and robustness of our segmentation approach by extensively evaluating it on 96 carotid arteries. Fifth, we evaluate the accuracy of the automatically extracted geometry measurements.

The remainder of this chapter is organized as follows: Section 2 describes the data and the method. Section 3 prepares the data acquisition protocol, reference standard, parameter optimization, and an evaluation of segmentation accuracy and carotid bifurcation geometry quantification are presented. We discuss the results and conclude this chapter in Section 4.

2.2 Methods

The data used in our work is from the Rotterdam Study [45] which investigates factors that determine the occurrence of cardiovascular, neurological, ophthalmological, endocrinological, and psychiatric diseases in elderly people. Two MR scans, BBMRI and PCMRA, are acquired of subjects with a vessel wall thickness larger than 2.5 mm in at least one of the carotid arteries, as determined with 2D ultrasound of the carotid arteries. The lumen intensity is suppressed in BBMRI, but enhanced in PCMRA. Our quantification procedure consists of four stages. In the first stage, the BBMRI and PCMRA scans are preprocessed to reduce intensity inhomogeneity and noise followed by an affine registration to geometrically align them. Second, the two centerlines are determined by finding the minimum cost path between one seed point from the common carotid artery and one in respectively the external and internal carotid artery. Third, the carotid artery lumen is segmented using a topology-preserving geodesic active contour approach which is initialized by the extracted centerlines. Fourth, the bifurcation angle and centerline tortuosity are quantified from the segmented carotid artery. An overview of the method is shown in Fig. 2.1, and details on all four stages are presented below.

2.2.1 Preprocessing

Preprocessing is applied to reduce the inherent intensity inhomogeneities and to suppress noise. The preprocessing includes three steps. First, we apply a bias field correction approach to BBMRI images as proposed by Sled et al. [106] to correct for intensity inhomogeneities. The parameters of the bias correction, such as the shrink factor and the number of fitting levels, are fixed and listed in Section 3. We do not correct the bias field for PCMRA as it suf-
fers less from intensity inhomogeneity than BBMRI. Optionally, an anisotropic edge enhancement diffusion filter [131] is employed to reduce image noise while preserving edges in both BBMRI and PCMRA. The parameters for denoising such as Gaussian gradient scale are fixed but different for BBMRI and PCMRA. The impact of performing denoising is evaluated in the experiments. Finally, to remove the inter-scan intensity variation, we apply an intensity normalization such that the images have zero mean and unit variance. All parameters in the preprocessing part are fixed and are described in the parameter selection section. Fig. 2.1 shows the BBMRI and PCMRA before and after preprocessing.

2.2.2 Centerline Extraction

The centerline extraction consists of two parts. First, the centerlines are determined between three manually annotated seed points (common, internal and external) with a cost function based on a medialness measure [37] and the similarity of the local image intensities to the image intensities at the position of the seed points [114]. Secondly, to improve the centerline accuracy in highly curved regions, the centerlines are refined by recomputing the minimum cost path after curved multi-planar reformatting (CMPR) perpendicular to the previous centerline.

The minimum cost path approach finds the path with minimal accumulated cost between the start and end seed points. The accumulated cost $E(C)$ is defined as:

$$E(C) = \int P(C(p)) |C'(p)| dp$$  \hspace{1cm} (2.1)

where $P(x)$ denotes the potential or cost at location $x$ and $p$ denotes the parametrization of the path $C$ between start and end point.

Cost Function and Minimum Cost Path

Our cost function includes two terms: medialness $m(x)$ [37] based on the gradient and a similarity term $s(x)$ based on the intensity. Both $m(x)$ and $s(x)$ give a high response in the center of the lumen and a low response in the background. The medialness is a multiscale measure which uses gradient information and ranges from 0 to 1. The exact definition of medialness can be found in [37]. The lumen similarity measure is based on the voxel intensity. Parameters that tune the contrast of the cost image are commonly incorporated in the
2.2. Methods

Cost definition because the path $C$ depends not only on the cost $P(C(p))$ but also on the curve length. We define the cost function as follows:

$$P(x) = \frac{1}{\epsilon + m(x)^\alpha s(x)^\beta}$$  \hspace{1cm} (2.2)

where $\epsilon$ is a small positive value to prevent singularities. The parameters $\alpha$ and
\( \beta \) control the contrast of the cost image, and their value will be optimized in the training stage. The two terms of the cost function are both based on multispectral MRI to improve tracking robustness. The multispectral medialness is defined to be the maximum medialness of the two images:

\[
m(x) = \max(m_{BB}(x), m_{PC}(x)) \quad ,
\]

where \( m_{BB} \) and \( m_{PC} \) denote the slice based medialness in BBMRI and PCMRA respectively. The slice based medialness calculation is based on the assumption that carotid arteries run approximately perpendicular to the transverse plane. This assumption will increasingly be satisfied through the centerline refinement procedure we propose in Section 2.2.2.

The intensity measure is defined as follows:

\[
s(x) = \max(s_{BB}(x), s_{PC}(x)) \quad ,
\]

where \( s_{BB} \) and \( s_{PC} \) are called lumen intensity similarity for BBMRI and PCMRA respectively. These measures are based on the assumptions that the lumen intensity is suppressed in BBMRI, enhanced for PCMRA, and normally distributed. Further, it is assumed that voxels have a 100% probability of being part of the lumen if its intensity is respectively lower (BBMRI) or higher (PCMRA) than the image intensity sampled at the seed points. Thus the lumen similarities for BBMRI and PCMRA can be defined as follows:

\[
s_{BB}(x) = \begin{cases} 
e^{-\frac{1}{2} \left( \frac{I_{BB}(x) - \mu_{BB}}{\sigma_{BB}} \right)^2}, & I_{BB}(x) > \mu_{BB} \\ 1, & I_{BB}(x) \leq \mu_{BB} \end{cases}
\]

and

\[
s_{PC}(x) = \begin{cases} 
e^{-\frac{1}{2} \left( \frac{I_{PC}(x) - \mu_{PC}}{\sigma_{PC}} \right)^2}, & I_{PC}(x) < \mu_{PC} \\ 1, & I_{PC}(x) \geq \mu_{PC} \end{cases}
\]

The standard deviations (\( \sigma_{BB} \) and \( \sigma_{PC} \)) and the mean intensities (\( \mu_{BB} \) and \( \mu_{PC} \)) are derived from a small sphere centered at the three seed points. The radius is 3.5 mm for the common carotid artery point and 2.5 mm for the external and internal carotid artery points. The lumen intensity similarity ranges between 0 and 1.

An example of the medialness and the lumen intensity similarity is shown in Fig. 2.2. Fig. 2.2(a) shows the medialness response of preprocessed BBMRA in Fig. 2.1 while Fig. 2.2(c) depicts the lumen intensity similarity response, Fig. 2.2(b) and Fig. 2.2(d) show corresponding response profile, which show that
2.2. Methods

Figure 2.2: An example of the original and preprocessed MRI: (a) medialness image, (b) profile of medialness image, (c) lumen intensity similarity, (d) profile of lumen intensity similarity. From red to white, the exponential increases from 1 to 4.

medialness provides better lumen center representation while lumen intensity similarity strongly suppresses the background signal.

Centerline Refinement through CMPR

After the first extraction step, the centerlines are not sufficiently accurate for two reasons: 1) the medialness is calculated in planes which are not always perpendicular to the vessel direction, and 2) there is a short-cut effect because the cumulative cost in Eq. 2.1 is determined by both the curve length and the cost $P(C(p))$. We can address both issues simultaneously by creating a new image stack in which the planes are sampled perpendicular to the minimum cost path from the first centerline tracking step. This resampling procedure is referred to as curved multi-planar reformatting (CMPR). A similar approach was presented by Heekeren et al. [124] to solve the short-cut property of minimum cost path algorithms. The difference between our work and the work by Van Heekeren et al. (2007) is that our method updates the cost image after every iteration whereas Van Heekeren et al. (2007) resampled the cost image defined in the first centerline extraction step. Another extension of our method
Chapter 2. Lumen Segmentation for Carotid Geometry Quantification in Multispectral MRI

Figure 2.3: Illustration of the CMPR generation: (a) CMPR stack in original space; (b) CMPR stack after reformatting.

is that we refine the initial centerline in 3D, while Van Heekeren et al. did it in 2D. We assume that the first centerline estimate is already in the vessel lumen, therefore we also use a slightly different cost function in the refinement iteration, which only depends on the medialness in the BBMRI. The reason for this choice is two-fold: medialness is better in localizing the lumen medial axis than the lumen intensity similarity and BBMRI yields a better lumen boundary. Since we already have a good initial centerline close to carotid lumen center, the lumen intensity term and PCMRA which are mainly for improving robustness are not needed in this step. The cost image in CMPR is therefore defined as:

\[ P(x) = \frac{1}{\epsilon + m_{BB\text{CMPR}}(x)^\gamma} \quad (2.7) \]

where \( \gamma \) controls the cost image contrast. This step is iterated until the centerline converges. Fig. 2.3(a) and Fig. 2.3(b) provide an example of the original image and the image stack generated by CMPR.

2.2.3 Lumen Segmentation

After preprocessing, BBMRI data still suffer from a residual intensity inhomogeneity and varying background. Hence the intensity of the fore- and background can not be described by a global model. Therefore, we prefer a segmentation approach using local image features over global features. Given the refined centerlines as initialization, we use a topology-preserving active contour [17, 41] to segment the carotid lumen. The topology preservation method is designed to prevent possible merging of the two branches in cases where they are very close to each other. This step is applied to the BBMRI, as it has higher image resolution and a better lumen representation than PCMRA.
We minimize the energy $E$ of a 3D surface $S$. The energy is defined as [19]:

$$E(S) = \iint P(I(S(u,v)))|S'(u,v)|dudv,$$  \hspace{1cm} (2.8)

where $S(u,v)$ is the 3D surface parametrized by $u,v$ and $P(I(S(u,v)))$ denotes the cost. The latter is usually inversely proportional to the gradient magnitude [17, 19]. However, owing to the limited resolution and contrast (shown in Fig.2.4(a)), we use an intensity based cost function $P(I(x))$, defined as the intensity difference to the estimated lumen boundary intensity $I_b(z)$ for slice $z$, where $z$ denotes the third element of $x$:

$$P(I(x)) = |I(x) - I_b(z)|. \hspace{1cm} (2.9)$$

The boundary intensity should lie between the fore- and background intensity:

$$I_b(z) = I_{\text{fore}}(z) + k(I_{\text{back}}(z) - I_{\text{fore}}(z)), \quad (0 < k < 1) \hspace{1cm} (2.10)$$

in which $I_{\text{fore}}(z)$ and $I_{\text{back}}(z)$ are the fore- and background intensity respectively, and $k$ is a parameter which controls the definition of lumen boundary intensity which will be optimized. The foreground intensity $I_{\text{fore}}(z)$ is defined per slice as the average intensity within a circle with radius $r_1$ centered around the centerline. The background intensity is estimated as the average over all voxels within a circle with radius of $r_2$ that have a local lumen similarity $s_{\text{local}}$ less than 0.5, with $s_{\text{local}}$ defined as:

$$s_{\text{local}}(x) = \begin{cases} e^{-\frac{1}{2} \left( \frac{I(x) - I_{\text{fore}}(z)}{\sigma} \right)^2}, & I(x) > I_{\text{fore}}(z) \\ 1, & I(x) < I_{\text{fore}}(z). \end{cases} \hspace{1cm} (2.11)$$

The standard deviation $\sigma$ is the average standard deviation of the lumen intensity in the training data.
Let $\phi$ be the embedding function of surface $S$, which is negative inside and positive outside. Optimization of Eq. 2.8 using gradient descent yields the following levelset evolution [17]:

$$\phi_t = P(I(x)) \kappa \nabla \phi + \nabla P(I(x)) \cdot \nabla (\phi),$$  \hspace{1cm} (2.12)

where $\kappa = \text{div} \left( \frac{\nabla \phi}{|\nabla \phi|} \right)$ is the mean curvature. In our application, the minimum curvature $\kappa_{\text{min}}$ is used as we are dealing with tubular structures [72]. The curvature term (first term of Eq. 2.12) is weighted by a parameter $c$ which controls surface smoothness. To prevent the internal and external branches from touching, the surface topology is preserved. We follow the approach of Han et al. [41] which evolves only the surface at simple points. A point is a simple point if its addition to or removal from the segmentation does not change its topology [61]. Usually a propagation term that speeds up the evolution is added [17], thus the levelset evolution becomes:

$$\phi_t = \begin{cases} cP(I(x)) \kappa_{\text{min}} |\nabla \phi| + P(I(x)) |\nabla \phi| + \nabla P(I(x)) \cdot \nabla \phi, & \text{if } x \text{ is a simple point} \\ 0, & \text{otherwise} \end{cases} \hspace{1cm} (2.13)$$

The two parameters $k$ and $c$ will be optimized in the experiments.

### 2.2.4 Quantification of Geometry

Lee et al. [66] found a significant relation between disturbed flow and proximal area ratio, proximal bulb size and local distal tortuosity. We therefore quantified these carotid geometry measures. Beside that, we also quantified the bifurcation angle and the tortuosity for the internal and external branches to facilitate their influence on clinical events, such as plaque stability.

**Carotid coordinate system:** The quantification of the bifurcation parameters requires a standard coordinate system. We use the coordinate system as described in [4]. Using VMTK, we first extracted the lumen centerlines from the segmentation by a minimum cost path approach. The cost is defined inversely proportional to the radius of the maximum inscribing spheres (MIS). All the MISs along the internal carotid artery (ICA) or external carotid artery (ECA) centerline generate a tubular surface. ICA0 (ECA0) is an intersection point of the ICA (ECA) centerline and ECA’s (ICA’s) tubular surface. Similarly, two downstream spheres centered at CCA00 and CCA01, which pass through ICA0 and ECA0 respectively, can be found. Shown in Fig. 2.5(a), CCA1 (ECA1, ICA1) is the center of a downstream (upstream) MIS which passes through CCA0 (ECA0, ICA0). CCA0n (ECA0n, ICA0n) can be determined in a similar
2.3 Experiments and Results

In this section we describe the data acquisition, the implementation details, the generation of a reference standard, as well as the evaluation of the centerline extraction, segmentation and geometry quantification. To study the influence of the denoising step on segmentation, we evaluated our methods on images with and without denoising.
Chapter 2. Lumen Segmentation for Carotid Geometry Quantification in Multispectral MRI

2.3.1 Data Acquisition

BBMRI images and PCMRA images were obtained from 49 subjects who were randomly selected from participants in the Rotterdam Study. The BBMRI images were acquired in the transverse direction with a Field Of View (FOV) of 13×13 cm², a matrix of 160×128, an in-plane pixel size of 0.51×0.51 mm² after zero padding in the Fourier domain, 0.9 mm slice thickness and 480 ms and 9.8 ms for repetition time (TR) and echo time (TE) respectively. The PCMRA images were scanned in the coronal direction and have a FOV of 18×18 cm², a matrix of 256×128, an in-plane pixel size of 0.7×0.7 mm² after zero padding in the Fourier domain, a slice thickness of 1.0 mm, a TR and TE of 13 ms and 4.3 ms respectively. In order to select representative data for training, image quality was visually assessed by a trained observer and the datasets were grouped into four classes according to image quality, i.e. bad (1), normal (17), good (29), and excellent (2). The single image with bad image quality was excluded from the study, as their image quality did not permit quantification of the bifurcation angle. All other scans from the 48 subjects (96 carotid arteries) were included in the experiments. The presence of flow artifacts was assessed visually by detecting regions of increased lumen intensity that was not attributed to wall thickening. 24 carotid arteries were found to have flow artifacts: 17 have artifacts in one slice, 2 have artifacts in 2 slices,
and the remaining ones have artifacts in 3-6 slices.

### 2.3.2 Software and Implementation

Affine registration from PCMRA to BBMRI was performed using Elastix [58]. The minimum cost path approach was performed simultaneously from the two seed points using Dijkstra's algorithm [30]. The topology preserving geodesic active contour was based on an ITK implementation [51]. The centerline evaluation software from Schaap et al. [94], and the segmentation evaluation software from Hameeteman et al. [39] and Hameeteman et al. [40] were used. The reference standard was annotated using in-house developed software [39] built with MeVisLab (http://www.mevislab.de).

### 2.3.3 Reference Standard

The 48 datasets were divided into a training set of 10 datasets (4 normal and 6 good, 4 carotid arteries have artifacts) and a test set of 38 datasets (13 normal, 23 good, 20 carotid arteries have artifact). To compare the accuracy with the inter- and intra-observer variability, we randomly selected another 15 datasets (5 normal, 9 good, 1 excellent) from the test set in which the inter- and intra-observer variability of segmentation and geometry quantification was determined (see Fig. 2.6). The second annotations for the intra-observer study were done three months after the first annotation. The observer annotated the centerlines for the entire clinically relevant region.

![Data composition in this work.](image)

Intra-observer variability is the variability between the first and the second annotations of the first observer. The inter-observer variability is the average
variability between the second observer’s annotation and the first observer’s two annotations. The accuracy of centerline extraction, lumen segmentation and geometry quantification is the average accuracy with respect to these three observations. To compare the geometries obtained from our automated segmentation to the manual ones, the average correlation was determined. We evaluated the segmentation method using two evaluation metrics: the Dice similarity coefficient (DSC) [29] and the mean absolute surface distance (MASD) [40].

2.3.4 Parameter Selection

We selected the end points of the manually annotated centerlines as the seed points for the centerline extraction. The fixed parameters in different steps of the algorithm are listed in Table 2.1.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Parameters</th>
<th>BB/PCMRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprocessing</td>
<td>shrink factor (N3)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td># of fitting levels (N3)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>scale (denoising) 1/0.7 (mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td># of scales (medialness)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>scale (medialness) 1 (mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td># of angles (medialness)</td>
<td>24</td>
</tr>
<tr>
<td>Centerline</td>
<td>max radius (medialness) 12 (mm)</td>
<td></td>
</tr>
<tr>
<td>extraction</td>
<td>min radius (medialness) 0 (mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMPR FOV 12×12(mm×mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMPR matrix 90×90</td>
<td></td>
</tr>
<tr>
<td>Segmentation</td>
<td>r1 1 (mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>r2 10 (mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>minimum RMS error 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td># of iterations 1000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>initial tube radius 1 (mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>connectivity 26</td>
<td></td>
</tr>
</tbody>
</table>

The parameters are optimized in a training session. Their optimization is described in the following section. Since the centerline accuracy may effect the segmentation accuracy, we also studied the effect of the initialization on the segmentation accuracy.
Parameter Optimization Experiments

The parameter optimization for centerline extraction consists of 2 steps. In the first step, the cost function is optimized by minimizing number of failures. A failure is defined as tracking into non-carotid arteries or by tracking from the external (internal) artery into the internal (external) artery. After selecting the combinations of scans (BBMRI and PCMRA) and measures (medialness and gradient) based on which the cost image yields the minimum number of failures, the values of $\alpha$ and $\beta$ are optimized for centerline accuracy. The parameter $\gamma$ is tuned in a similar way in the second CMPR stage. The parameters $\alpha$, $\beta$ and $\gamma$ were all varied from 1 to 4 in steps of 1.

The criterion for optimizing $k$ and $c$ is maximizing DSC. We tune $k$ from 0.3 to 0.8 in steps of 0.05 and $c$ logarithmically from $1e-5$ to $1e-1$ in 5 steps.

We also investigate the influence of the centerline in the segmentation results. Here, the centerlines obtained after one, two or three CMPR iteration steps (which have an accuracies of 0.74 mm, 0.36 mm and 0.33 mm respectively) are used for initializing segmentation. In addition to this, we also performed segmentations based on manual centerlines. We fixed $c$ and trained $k$ for each initialization using the same above-mentioned training scheme and compare the optimal segmentation results for different initial centerlines.

Parameter Optimization Results

Table 2.2 lists the average number of failed centerline extractions over all combinations of $\alpha$ and $\beta$ for each of the cost image combinations (only BBMRI, only PCMRA, multispectral MRI) for images with and without denoising. The average number of failures instead of minimum number of failures is used in this step to increase the robustness. It shows that, in all cases, the number of failures is reduced by adding the intensity similarity term. In the multispectral case with denoising, non of the combinations of $\alpha$ and $\beta$ give failures in centerline extraction. Without denoising, the cost image based on both medialness and lumen intensity similarity in PCMRA performs best.

Fig. 2.7(a) and Fig. 2.7(b) show the variation of the mean centerline distance (MCD) as a function of $\alpha$ and $\beta$ for images with and without denoising respectively. For images with denoising, increasing $\alpha$ decreases the MCD while $\beta$ does not significantly influence the MCD. For images without denoising, increasing $\alpha$ and $\beta$ both decreases the MCD. Centerline extraction in images with denoising (0.74 mm) achieves higher accuracy than in images without denoising (0.82 mm). In all subsequent experiments, $\alpha$ and $\beta$ are set to 4.

The parameter $\gamma$ has little influence on centerline accuracy after the first iter-
Table 2.2: Average number of failures for the different images and cost functions, with and without denoising.

<table>
<thead>
<tr>
<th>Images</th>
<th>Cost Image</th>
<th>With d</th>
<th>Without d</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBMRI</td>
<td>medialness</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>medialness+intensity</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>PCMRA</td>
<td>medialness</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>medialness+intensity</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Multispectral</td>
<td>medialness</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>medialness+intensity</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 2.7: MCD variation with respect to $\alpha$ and $\beta$ for images with denoising (a) and for images without denoising (b).

In the first iteration, PCMRA without denoising produces less accurate centerlines than a combination of BBMRI and PCMRA with denoising. However, in the subsequent iterations, the centerlines from images with and without denoising, thus $\gamma$ is set to 1 in each iteration.

Fig. 2.8 shows the centerline accuracy as a function of the number of iterations.
ing are both improved and the average mean centerline distance converges to the inter-observer variability on average after 2 iterations. Thus, for centerline extraction, using our iterative scheme, image denoising is not required.

Figure 2.8: MCD as a function of iteration time for images with and without denoising.

Segmentation initialized by centerlines after two iterations of CMPR (MCD = 0.33 mm) were used to optimize the value for $c$ and $k$ using images with and without denoising. For images without denoising, the segmentation for two carotid arteries leak when $c$ is smaller than 0.01. Fig. 2.9(a) and Fig. 2.9(b) show the optimization of $c$ and $k$ w.r.t DSC after excluding the failed segmentation. Fig. 2.9(c) shows that under the condition of successful segmentation, optimal values for $c$ are smaller for images with denoising than for images without denoising. The maximum DSC is 0.86 for images with denoising and 0.84 for images without denoising at $c = 0.01, k = 0.60$ and $c = 0.01, k = 0.65$ respectively.

We also investigated the segmentation accuracy as function of centerline initialization. The average DSC was similar for manual centerlines and centerlines obtained after one or two iterations (Table 2.3). It yields an MCD of 0.36 mm and 0.33 mm with $k$ optimized at 0.6 for these three cases. In the final algorithm that is evaluated on the test set, centerlines from the third centerline iteration were used for initialization.

In conclusion, based on the parameter optimization stage, we choose to use both BBMRI and PCMRI, $\alpha = \beta = 4, \gamma = 1, k = 0.6, c = 0.01$; we included denoising in the preprocessing, and used centerlines from the third iteration for the algorithm evaluation.
Chapter 2. Lumen Segmentation for Carotid Geometry Quantification in Multispectral MRI

Figure 2.9: Optimization results of $k$ and $c$ in segmentation: (a) training on image with denoising, (b) training on image without denoising, (c) profile of the optimization matrix at $k = 0.6$ and $k = 0.65$ for image with denoising and without denoising respectively.

Table 2.3: DSC as a function of $k$ for three different centerline initializations from each iteration step of centerline tracking and manual centerline based on images with denoising at $c = 0.01$.

<table>
<thead>
<tr>
<th>iteration</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>manual</th>
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<tbody>
<tr>
<td>MCD (mm)</td>
<td>0.74</td>
<td>0.36</td>
<td>0.33</td>
<td>manual</td>
</tr>
<tr>
<td>$k$</td>
<td>0.65</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>DSC</td>
<td>0.84</td>
<td>0.86</td>
<td>0.86</td>
<td>0.86</td>
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</table>

2.3.5 Lumen Centerline Extraction

The method with its optimized parameters was applied to images with denoising. For the set of 30 carotid arteries with inter- and intra-observer variability,
centerline extraction failed in one carotid artery. The average centerline MCD for the 29 successful cases was 0.30 mm (min MCD = 0.58 mm, max MCD = 0.15 mm), which is comparable to the inter observer variability (0.32 mm) and close to intra-observer variability (0.27 mm).

For all 76 carotid arteries, the method successfully extracted 150 out of the 152 centerlines. The only two failures were due to a high curvature in one of branches or touching between the internal and the external branches. In the first step, the average MCD was 0.73 mm (min MCD = 0.72 mm, max MCD = 0.14 mm) and after minimum cost path refinement using CMPR, the average MCD of the 150 centerlines was reduced to 0.36 mm after one iteration. On average, the MCD of extracted centerline converges to 0.33 mm after two iterations, which is comparable to the inter-observer variation after two iterations. The 18 out of 74 cases having flow artifacts in the carotid arteries yield a MCD of 0.37 mm, whereas in the other cases, the MCD is 0.31 mm. An example of the centerline extraction is shown in Fig. 2.10(a).

### 2.3.6 Lumen Segmentation

We applied the lumen segmentation with the optimized parameter settings for $k$ and $c$ to the testing datasets and quantitatively evaluated the segmentation accuracy by comparing the segmentation results to the annotated surfaces of the first observer. Shown in Table 2.4, for the set of 29 carotid arteries successfully segmented, the average DSC was 0.89 (max DSC = 0.94, min DSC = 0.81), which is close to the inter-observer variability (0.92). The average MASD was 0.29 mm (max MASD = 0.54 mm, min MASD = 0.13 mm), which is close to the inter observer variability (0.23 mm). For the 18 of 74 cases having flow artifacts in the carotid arteries, the DSC is 0.87, and the MASD is 0.36 mm. Whereas the cases without image artifacts have a DSC of 0.88 and a MASD of 0.28 mm.

For the 74 carotid arteries whose centerlines were successfully extracted, the average DSC is 0.89 (max DSC = 0.94, min DSC = 0.69), MASD is 0.31 mm (max MASD = 0.90 mm, min MASD = 0.15 mm). An example segmentation with DSC = 0.89 is shown in Fig. 2.10(b) to Fig. 2.10(e).
Table 2.4: Evaluation of centerline extraction MCD, segmentation DSC, MASD and the Pearson correlation coefficient between bifurcation angles, proximal area ratio, proximal bulb size as well as SOAM obtained from automatic segmentation and manual annotations on 30 carotid arteries, intra: intra-observer variability, inter: inter-observer variability, $r_{BA}$: the Pearson correlation coefficient of bifurcation angle. For 30 carotid arteries which have multiple annotations, $r_{PAR}$: the Pearson correlation coefficient of proximal area ratio, $r_{PBS}$: the Pearson correlation coefficient of proximal bulb size, $s_{LDM}$: the Spearman correlation coefficient of the local DM, $s_{IDM}$: the Spearman correlation coefficient of internal DM, $s_{EDM}$: the Spearman correlation coefficient of external DM, $r_{LSOAM}$: the Pearson correlation coefficient of the local SOAM, $r_{ISOAM}$: the Pearson correlation coefficient of internal SOAM, $r_{ESOAM}$: the Pearson correlation coefficient of external SOAM.

<table>
<thead>
<tr>
<th>segmentation accuracy</th>
<th>quantification accuracy</th>
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<tbody>
<tr>
<td>MCD (mm) DSC MASD (mm)</td>
<td>$r_{BA}$ $r_{PAR}$ $r_{PBS}$ $s_{LDM}$ $s_{IDM}$ $s_{EDM}$ $r_{LSOAM}$ $r_{ISOAM}$ $r_{ESOAM}$</td>
</tr>
<tr>
<td>intra 0.27 0.94 0.18</td>
<td>0.68 0.98 0.94 0.97 0.99 0.97 0.97 0.93 0.93</td>
</tr>
<tr>
<td>inter 0.32 0.92 0.23</td>
<td>0.79 0.95 0.91 0.87 0.95 0.93 0.94 0.83 0.93</td>
</tr>
<tr>
<td>auto 0.33 0.89 0.31</td>
<td>0.71 0.83 0.90 0.83 0.76 0.83 0.91 0.72 0.83</td>
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</table>
Figure 2.10: Example of (a) centerline extraction (first step 0.74 mm, forth step 0.31 mm) and (b) lumen segmentation (DSC=0.89), (c) slice A, (d) slice B, (e) slice C. Green: manual annotations for centerlines and segmentation, red: automatically obtained results of centerline extraction and segmentation, yellow: the centerline from the first step.
2.3.7 Geometry Quantification

This section presents the result of quantification of nine geometry measurements. Quantifications from the datasets with imaging artifacts are plotted in red, while quantifications from the datasets without imaging artifacts are plotted in gray. Two plots, the scatter plot and the Bland Altman plot, are shown for all measurements; we calculated the 95% slope confidence interval to check whether the slope is significantly different from unit slope. An independent t test is performed for each measure to check whether there is a significant bias in the automated quantification compared to the manual quantification.

Bifurcation Angle

Carotid bifurcation angles were quantified using both the manual segmentation and the automatic segmentation methods. Fig. 2.11(a) shows the scatter plot and the Bland and Altman plot of the automatically obtained angles and the angles extracted by the first observer. The Pearson correlation coefficient between the angles obtained with our method and the first observer for 94 carotid arteries is 0.76. The slope of Pearson correlation is significantly different from unit slope, as the unit slope does not lie within the 95% slope confidence interval, see Table 2.5.

Table 2.4 indicates that for 30 carotid arteries which have inter- and intra-observer annotations, this correlation is close to the inter-observer correlation. Fig. 2.11(b) shows the automatic bifurcation angle has a lower mean and only 5 out of 94 carotid arteries have bifurcation angles which are outside the mean ± 1.96× standard deviation (std.dev) range. Even though the slope is significantly different from unit slope, the automatic bifurcation angle quantification is not significantly biased, as the mean from the automatic bifurcation angle is not significantly different from that of manual bifurcation angle quantification, see Table 2.6.

Proximal Area Ratio and Proximal Bulb Size

Out of the 94 successfully extracted carotid arteries, 8 carotid arteries did not contain CCA2, for 15 segmentations ICA1 was still in the bifurcation bulb, and for 31 segmentations ECA1 was similarly not usable. Of the 94 manual carotid arteries, 8 did not contain CCA2, for three segmentations the ICA1 and for 20 segmentations the ECA1 are not usable because they are still in the bifurcation bulb. After removing those cases where CCA1, ICA1 or ECA1 are not available for quantification, we compared the manual area ratio and proximal bulb size with the automatic ratio and proximal bulb size.
2.3. Experiments and Results

Figure 2.11: Scatter plots of (a) bifurcation angle, (c) proximal area ratio, (e) proximal bulb size and Bland-Altman plots of (b) bifurcation angle, (d) proximal area ratio and (f) proximal bulb size of manual and automatic segmentations.

Fig. 2.11(c) and Fig. 2.11(d) show the scatter plot and Bland-Altman plot of proximal area ratio. Since the proximal area ratio is not normally distributed, we calculated the Spearman correlation coefficient, which is 0.90. The slope is significantly different from unit slope, as shown in Table 2.5. Out of the 53 carotid arteries where CCA1, ICA1 and ECA1 can be determined correctly, two carotid arteries have an proximal area ratio outside the mean ± 1.96× std.dev
range. The automatic proximal area ratio quantification is not significantly biased, see Table 2.6.

Fig. 2.11(e) and Fig. 2.11(f) show the scatter plot and Bland-Altman plot of proximal bulb size respectively. The Pearson correlation coefficient is 0.88. Out of the 66 carotid arteries whose CCA1 and ICA1 are available for proximal bulb size quantification, three carotid arteries have a proximal bulb size outside the mean ± 1.96× std.dev range. The slope of proximal bulb size is significantly different from unit slope, the automatic proximal bulb size quantification is not significantly biased, as shown in Table 2.6.

For the 30 carotid arteries for which three annotations are present, we also analysed the inter- and intra-observer variability. The cases where the second or third annotation does not permit a quantification, because of the above reasons, are excluded. Since for these datasets with second and third annotations, the proximal area ratio and proximal bulb size are normally distributed, we calculated the Pearson correlation coefficient. The Pearson correlation coefficients of proximal area ratio and proximal bulb size between manual annotations are listed in Table 2.4, the Pearson correlation of proximal area ratio between automatic segmentation and manual segmentation is close to those between manual annotations between different observers.

**Tortuosity**

In the automatic quantification, the centerline extracted by the minimum cost path approach is closer to the manual centerline than the centerline extracted from the segmented surface in VMTK (0.33 mm vs. 0.50 mm). The manual tortuosity is quantified from a centerline extracted from manual surface by VMTK. In order to avoid a large centerline variation caused by small segmentation variation, the centerlines obtained from VMTK are smoothed with scale of 1 and iteration time of 1000. All the manual and automatic centerlines are sampled with a step-size of 0.1 mm. Based on this we quantified centerline tortuosity using the centerline extracted by the method described in Section 2.2. However, the end points of the local centerline, i.e. ICA5 and CCA2 were determined using VMTK. In 94 carotid arteries, the manual segmentations of 6 carotid arteries do not have an internal branch long enough to provide ICA5, while the automatic segmentation of 12 carotid arteries are not long enough to provide ICA5. Similar to the proximal area ratio calculation, we removed the cases where ICA5 and CCA2 could not be correctly determined. This resulted in 74 carotid arteries whose manual and automatic local centerlines were usable for quantification.

Fig. 2.12 shows the scatter plots and Bland-Altman plots of DM for the local centerlines, internal centerlines and external centerlines. Because the DM is
2.3. Experiments and Results

not normally distributed, we calculated the Spearman correlation coefficient. The Spearman correlation coefficients for local, internal and external DM are 0.91, 0.92 and 0.94 respectively. Table 2.5 shows that the slopes of the three DM measurements are significantly different from unit slope. Bland-Altman plots show that for local centerline DM, 2 out of 74 centerlines are outside the range of the mean $\pm 1.96 \times \text{std.dev}$, for internal centerline DM, 3 out of 94 centerlines are outside the range of the mean $\pm 1.96 \times \text{std.dev}$, and for external centerline DM, 6 out of 94 centerlines are outside the range of the mean $\pm 1.96 \times \text{std.dev}$. Table 2.6 shows that there is an overestimation in automatic local DM quantification versus manual DM quantification, but the internal and external DM are not significantly biased.

We also analysed the inter- and intra-observer variability. The Spearman correlation coefficient of the three DM measures between manual annotations are listed in Tab. 2.4. The Spearman correlation coefficient of local DM between automatic segmentation and manual segmentation is close to that between manual annotations between different observers. The Spearman correlation coefficients of internal and external DM between automatic segmentation and manual segmentation are lower than that between manual annotations between different observers.
Table 2.5: 95% confidence interval of slope for 9 measurements. CI: confidence interval.

<table>
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<tr>
<td>95% CI</td>
<td>0.74±0.14</td>
<td>0.65±0.09</td>
<td>0.80±0.09</td>
<td>1.27±0.13</td>
<td>1.13±0.03</td>
<td>1.22±0.05</td>
<td>1.07±0.15</td>
<td>1.02±0.12</td>
<td>1.02±0.10</td>
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Table 2.6: Results of independent t test between automatic and manual quantifications for 9 measures. 95% confidence interval, 0.05 level

<table>
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<tbody>
<tr>
<td>$p_{\text{variance}}$</td>
<td>0.18</td>
<td>0.37</td>
<td>0.16</td>
<td>0.03</td>
<td>0.21</td>
<td>0.57</td>
<td>0.01</td>
<td>0.30</td>
<td>0.16</td>
</tr>
<tr>
<td>$p_{\text{mean}}$</td>
<td>0.40</td>
<td>0.06</td>
<td>0.09</td>
<td>0.00</td>
<td>0.06</td>
<td>0.30</td>
<td>0.00</td>
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Fig. 2.13 shows the scatter plots and Bland-Altman plots of SOAM for local centerlines, internal centerlines and external centerlines. Because the SOAM is not normally distributed, we calculated the Spearman correlation coefficient. The local SOAM, internal SOAM and external SOAM have a Spearman correlation coefficient of 0.85, 0.80 and 0.88 respectively. Table 2.5 shows that the SOAM quantifications have a slope not significantly different from unit slope. Bland-Altman plots show that for local centerline SOAM, 3 out of 74 centerlines are outside the range of the mean ± 1.96 × std.dev, for internal centerline SOAM, 3 out of 94 centerlines are outside the range of the mean ± 1.96 × std.dev, and for external centerline SOAM, 4 out of 94 centerlines are outside the range of the mean ± 1.96 × std.dev. Table 2.6 shows that there is a bias in the automatic SOAM quantifications versus the manual SOAM quantifications, and the Bland-Altman plot of SOAM measurements shows that the three SOAM measurements are overestimated.

We analyzed the inter- and intra-observer variability of Pearson correlation coefficient for the 30 carotid arteries with the second and third annotations. The cases where the second or third annotation do not permit a quantification of local tortuosity, because of the above reasons, are excluded. The correlation coefficients of SOAM for internal centerline, external centerline and local centerline between manual annotations are listed in Tab. 2.4, the correlation coefficient of SOAM between automatic and manual segmentation is close to that between manual annotations of different observers.

## 2.4 Discussion and Conclusion

We presented a semi-automatic segmentation method for extracting the carotid artery bifurcation from multispectral non contrast enhanced MRI data followed by quantification of the carotid bifurcation geometry. First, centerline tracking is performed using both BBMRI and PCMR for the sake of robustness. Subsequently, the centerline is refined by iteratively applying the minimum cost path approach in a CMPR version of the BBMRI image. The refined centerline is then used to initialize a topology preserving levelset evolution steered by intensity information from the BBMRI image. The centerline tracking and lumen
Figure 2.12: Tortuosity of local, internal and external branches from segmented and manual carotid lumen: scatter plots of (a) local DM, (c) internal DM, (e) external DM; Bland-Altman plots of (b) local DM, (d) internal DM and (f) external DM from manual and automatic segmentations.

The optimization showed that the centerline extraction method is insensitive to changes in two parameters, namely the parameter that controls the contrast of the centerline tracking cost function \( \beta \) for images with denoising and the parameter that controls the contrast in cost image used for the centerline re-
2.4. Discussion and Conclusion

For centerline tracking, incorporating PCMRA to construct a multispectral cost function improves the robustness for images with and without denoising. Probably, the use of both images limits the influence of imaging artefacts or compensates for regions with lower contrast to noise present in one of the scans. The centerline refinement step increases the accuracy of centerline extraction by reducing the short-cut property of minimum cost path approach.

Figure 2.13: Tortuosity of local, internal and external branches from segmented and manual carotid lumen: scatter plots of (a) local SOAM, (c) internal SOAM, (e) external SOAM; Bland-Altman plots of (b) local SOAM, (d) internal SOAM and (f) external SOAM of manual and automatic segmentations.
For segmentation, the optimal value for the parameter $k$, which determines the boundary criteria, is close to 0.5. This indicates that the full width half maximum criteria, that was found to be a good boundary criterion in CEMRA [49] also appears to hold for BBMRI. The optimal curvature weighting parameter $c$ is smaller for images with denoising than images without denoising. This can be explained by the curvature smoothing behaviour of the denoising, which reduces the need of smoothing in the levelset evolution. In the experiments we found that denoising does not change centerline extraction accuracy. The denoising step slightly improves segmentation accuracy. A similar effect of adding a denoising step is also found in levelset based segmentation of cerebral aneurysms by [34].

We found that our method performs slightly better in the images without artefacts than in images with artefacts, but the accuracy of centerline extraction and lumen segmentation are still close to the inter-observer variability. The image artefacts do not affect the geometry quantification. The centerline extraction robustness may be influenced if there is a high variation around the seed point, but this influence is not observed in the data presented in this chapter. In the segmentation, a local sigma could improve the segmentation, but since the estimation of background is obtained in a substantially large area, that difference will not cause a large difference in background intensity estimation.

The evaluation results show that 94 of 96 carotid arteries are successfully segmented. The centerline extraction is achieved with an accuracy comparable to the inter-observer variability and close to the intra-observer variability. The segmentation method achieves subvoxel accuracy which is close to inter-observer variability. Our method is the first which is extensively validated on centerline accuracy, segmentation accuracy and carotid geometry quantification accuracy in multispectral MRI. Previously published methods have either received limited quantitative evaluation [134, 64, 52], no evaluation for lumen segmentation [1], or evaluation has primarily focused on lumen area [134], vessel wall area [64] or distance between corresponding points [52]. It is not possible to compare results between studies owing to differences in imaging modalities and scanning sequences used. However, carotid segmentation from CTA has been evaluated extensively in a challenge [40]. Although the data is different and the resolution of the CTA is higher than the resolution of our MRI data, our results (DSC) are in the same range of the best performing methods in that challenge.

The carotid bifurcation geometry quantification results based on the optimized automatic segmentation show that the automatic bifurcation angle is in the uncertainty range of mean $\pm 1.96 \times \text{std.dev}$ for over 89 of 94 carotid arteries respectively. The correlation between manual and automatic bifurcation angles is similar to the inter- and intra-observer correlation. Less than 6 carotid arteries have a proximal carotid area ratio or bulb ratio outside range of mean $\pm 1.96 \times$
2.4. Discussion and Conclusion

std.dev. For local centerlines, internal centerlines and external centerlines, less than 5 carotid arteries have a Distance Metric or Sum Of Angle Metric outside range of mean ± 1.96× std.dev. The local, internal and external SOAM as well as local DM are significantly overestimated. This is because our automatic centerline is less smooth than the centerline extracted from manual surface. The bias in the SOAM measures can be correctly by subtracting the bias, as the slopes of SOAM measures are very close to unit slope, the bias is constant. This bias does not strongly influence studying the association between these measurements and clinical events, as for such associations the correlation is relevant.

There are some limitations in our work. First, as the data of our study are acquired in the context of a population study, a non contrast enhanced MRI protocol was used. As a consequence, the lumen segmentation may include calcified plaques, which also appear black on BBMRI scans. A plaque segmentation and classification algorithm is part of future work. Second, the data in this chapter have been obtained in one center. Applying this method to BBMRI scans acquired with different imaging protocols may need parameter retraining. Last, in some cases the proximal area ratio or proximal bulb size are not able to evaluate for manual or automatic segmentations.

To conclude, the presented method determines carotid artery centerlines with an accuracy comparable to the inter-observer variability and segments the carotid artery lumen with an accuracy close to the inter-observer variability. Carotid geometry quantification measurements obtained from the automatic segmentation lie in the range of inter- and intra observer variability. The method thus has large potential to be used for automatic geometry quantification for carotid arteries in multi spectral MRI data.
Chapter 2. Lumen Segmentation for Carotid Geometry Quantification in Multispectral MRI

The estimation of background intensity can cause a large difference in background intensity estimation. The accuracy of segmentation can be improved by using a background intensity estimation technique. The evaluation of segmentation accuracy in multispectral MRI has primarily focused on lesion area, plaque volume, and plaque volume index in the last few years. However, current methods for segmentation accuracy evaluation (114, 44, 62) do not provide comprehensive evaluation of segmentation accuracy in multispectral MRI. Previously published methods have either focused on lesion area, plaque volume, or plaque volume index. However, current methods for segmentation accuracy evaluation do not provide comprehensive evaluation of segmentation accuracy in multispectral MRI.
Chapter 3

Lumen Segmentation and Stenosis Quantification in CTA

The degree of stenosis is an important biomarker in assessing the severity of cardiovascular disease. The purpose of our work is to develop and evaluate a semi-automatic method for carotid lumen segmentation and subsequent carotid artery stenosis quantification in CTA images. We present a semi-automatic stenosis detection and quantification method following lumen segmentation. The lumen of the carotid arteries is segmented in three steps. First, centerlines of the internal and external carotid arteries are extracted with an iterative minimum cost path approach in which the costs are based on a measure of medialness and intensity similarity to lumen. Second, the lumen boundary is delineated using a level set procedure which is steered by gradient information, regional intensity information and spatial information. Special effort is made in adding terms based on local centerline intensity prior so as to exclude all possible plaque tissues from the segmentation. Third, side branches in the segmented lumen are removed by applying a shape constraint to the envelope of the maximum inscribed spheres of the segmentation. From the segmented lumen, we detect and quantify the cross-sectional area-based and cross-sectional diameter-based stenosis degrees according to the NASCET criterion. The method is trained and tested on a publicly available database from the cls2009 challenge. For the segmentation, we obtain a Dice similarity coefficient of 90.2% and a mean absolute surface distance of 0.34 mm. For the stenosis quantification, we ob-

This chapter is based on:
tain an average error of 15.7% for cross-sectional diameter-based stenosis and 19.2% for cross-sectional area-based stenosis quantification. With these results, the method ranks second in terms of carotid lumen segmentation accuracy, and first in terms of carotid artery stenosis quantification.
3.1 Introduction

The latest report from WHO shows that cardiovascular diseases are the leading causes of death and disability in the world [77]. Atherosclerosis, a disease of the vessel wall, is one of the main causes of stroke and cardiac attack. The degree of stenosis in the internal carotid arteries is an important factor in grading cardiovascular disease severity. It also determines the treatment plan for carotid atherosclerosis. In the past digital Subtraction Angiography (DSA) was the diagnostic test to assess the severity of stenosis. The invasive nature of this procedure and the small, but clinically relevant complications has promoted the introduction of less invasive workup of patient with ischemic stroke. Nowadays Doppler Ultrasound is the standard imaging modality followed by MRA or CTA as a confirmatory test for the assessment of atherosclerotic carotid artery disease. CTA was found to be an accurate modality for the detection of severe carotid artery disease, especially for detection of occlusions [59]. For diagnosis and treatment planning, accurate stenosis quantification on CTA would be required. We aim to develop a semi-automatic carotid lumen segmentation and stenosis grading method in CTA.

Previous work on stenosis detection and grading in CTA. There are three criteria for quantifying the carotid stenosis degree, one established by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [6], one established by the European Carotid Surgery Trial (ECST) [129], and the Common Carotid (CC) method [127]. In (semi-)automatic quantification, the NASCET is commonly used [40, 97], in which the reference vessel diameter is defined at a location distal to the stenotic part of the vessel. Stenosis can be quantified based on the cross-sectional area (CSA) or cross-sectional diameter (CSD). Scherl et al. [97] first performed an internal carotid branch segmentation and then quantified the stenosis degree at manually annotated positions. Similarly, Zuluaga et al. [135] performed segmentation before stenosis detection and grading. They located the stenosis at the centerline location where the CSA is minimal. Kelm et al. [56] estimated the CSA curve for coronary arteries by a regression model using features from a cylinder around the extracted centerline points. We choose to perform an accurate segmentation before stenosis quantification.

Previous work on lumen segmentation: Lesage et al. [67] reviewed most of the recent vessel lumen segmentation methods for contrast enhanced imaging modalities (MRA and CTA) and categorized them according to their vessel extraction schemes, vascular models and image features. Several extraction schemes can be used for vessel segmentation, such as active shape/appearance models [24, 28], graph cuts [12] and level sets, including level sets using boundary information [72], using global regional information [22] and using variational
local regional information [68, 69, 65]. Vessels are usually modeled as tubular structures [35, 93, 72]. The tubular pattern is maintained by minimizing the minimal principal curvature in level sets [72] or by restricting the distance to centerlines in graph cuts [38].

Graph cuts [38, 95, 48] and level sets [75, 113, 62, 97, 116] are the two main extraction schemes for carotid lumen segmentation in CTA. Active Shape Models are not often applied due to the bifurcation of carotid arteries. A common initialization of these two schemes is the carotid artery centerline, which can be manual or (semi-) automatically extracted.

Scherl et al. [97] extended the Chan-Vese [22] model by adding an intensity based regularization term to remove calcium from the segmentation. The regularization term is based on a global lumen intensity estimation, which may not be realistic due to non-uniformity of the contrast agent. This method was evaluated on 10 internal carotid branches. Krissian et al. [62] also used the level sets extraction scheme steered by gradient magnitude information. Gülsün et al. [38] segmented the carotid arteries using a graph cut approach [13]. The novelty in their work is that they normalized the edge weight by the distance to centerlines to remove non-isolated topology caused by side branches or nearby veins. Manniesing et al. [75] utilized both gradient magnitude and intensity information to steer a level set evolution. Tang et al. [111] combined gradient magnitude information with a centerline intensity prior to segment carotid artery lumen while excluding calcium and soft plaque tissues. The aforementioned methods are all initialized by a semi-automatically extracted centerline. Ukwatta et al. [116] combined local intensity regional energy defined under a variational framework, together with global intensity regional energy, boundary energy and energy that encourages the boundary to pass through anchor points to segment the lumen and outer vessel wall of carotid arteries in 3D Ultrasound. Their method was evaluated on 231 transverse 2D image slices from 21 subjects.

Plaques, especially calcified plaques, pose challenges for lumen segmentation. Methods used for calcium exclusion can be divided into three types: excluding as part of a preprocessing step, [96, 74], in the segmentation step [97, 38], or as a post-processing step. Schaap et al. [96] suppressed calcium using intensity based kernel regression. In this method, hyper-intense areas are labelled as outliers and those areas are assigned an intensity which is much lower than the normal lumen intensity. Manniesing et al. [74] applied a mask to remove calcium and bone. Scherl et al. [97] segmented calcium and lumen simultaneously using a modified Chan-Vese model in which calcium is removed by an intensity-based regularization term. Gülsün et al. [38] excluded calcium by setting the ascending gradient from the centerline to zero. Cuisenaire et al. [27] removed the calcium by applying a threshold to the segmented foreground. In all these methods, only Scherl et al. [97] explicitly proposed a way to remove the entire
calcium and voxels around the calcium which has similar intensity to lumen but not lumen.

There has been some previous work on suppressing outliers (side branches) from lumen segmentation. Schaap et al. [95] removed outliers in a post-processing step by performing a robust kernel regression (both longitudinal and cross-sectional) on the distance of surface points to the centerline. The performance of the method was not evaluated on arteries with asymmetric stenoses. The second principal curvature is also a crucial feature in detecting side branches. Wijk et al. [125] removed protrusions from the colon surface by minimizing the second principal curvature flow. Even though it is possible to steer a level set evolution using curvature flow [73], in our task, this method is not suitable since the surface in the distal branches have a curvature that is similar to that in the side branches. Thus the distal part of external/internal carotid artery will shrink with the same speed as the side branches.

In this chapter, we present a semi-automatic stenosis detection and stenosis grading method based on accurate lumen segmentation which requires minimal user interaction. Our segmentation method excludes soft and hard tissues but also voxels around calcium by integrating a localized centerline intensity prior into a level set evolution scheme to guarantee sub-voxel accuracy. The method consists of three stages. First, the centerlines of the internal and external branches are extracted by a minimum cost path approach between user specified seed points. The cost image is defined by a measure of medialness and lumen intensity similarity to lumen. The centerlines are refined [113] to achieve an accuracy comparable to inter-observer variability, especially in curved regions, with cost defined in an image after hyper-intense suppression (suppressed using the initial centerlines). Second, we extend the Geodesic Active Contour [17, 72] segmentation method by combining it with regional intensity information and spatial information. In this way both the plaques and the voxels around calcium which have a similar intensity to lumen can be excluded successfully from the segmented lumen. Third, we remove side branches (mainly occurring in the distal part) by imposing a shape constraint to the envelope of maximum inscribed spheres.

Compared to previous segmentation methods, our paper has four main contributions. First, we add a local regional intensity term besides the Geodesic Active Contour approach to exclude nearby background such as plaques from segmentations. Second, we propose a spatial regularization term in the level set energy function to exclude voxels around calcium which have a similar intensity to that of the lumen. Third, we remove side branches in a post-processing step by imposing a shape constraint. Fourth, we evaluate the proposed method extensively using data of 56 carotid arteries from a publicly available dataset.

this chapter is organized as follows: Section 2 describes the method. Section 3
describes the data, the parameter optimization and the results. We discuss the results and conclude in Section 4.

3.2 Segmentation and Quantification Method

Carotid arteries originate from the aorta and split in the neck into the external and internal carotids. The proposed segmentation method requires three seed points: one in the internal, one in the external and one in the common carotid branches respectively. The internal and external centerline are extracted from the three seed points and used for initialization in the subsequent segmentation. We quantify stenosis based on the segmented lumen of carotid artery. The following subsections describe each step for the segmentation and stenosis grading.

3.2.1 Centerline Extraction

Centerlines are extracted in two steps. First, initial centerlines are extracted by a minimum cost path approach [30] approach between user-supplied seed points. We define the cost, which is used to compute the minimum cost path, as the inverse of the product of a slice-based medialness term [37] and a term indicating how similar a voxel is to the lumen intensity. The similarity term, which is close to one inside the lumen and close to zero in the background, is used to prevent centerline tracking through background. The initial centerlines extracted by the minimum cost path approach have two drawbacks: 1) they take short cuts (following the inner curve) in curved regions and 2) they tend to shift towards calcified regions. To address the first drawback, the extracted centerline is then iteratively refined by repeating the minimum cost path approach in a curved multi-planar reformatted image stack generated perpendicular to the centerline from the previous iteration. More details of this approach are provided in [113, 124]. To address the second drawback, we suppress hyper-intense regions as follows:

\[
I_p(x) = \begin{cases} 
I(x), & \text{if } I(x) < I_c(x) + \sigma_c \\
I_c(x) - (I(x) - I_c(x)), & \text{otherwise.} 
\end{cases}
\]  

(3.1)

where \(I_p(x)\) is the intensity after hyper-intense suppression, \(I_c(x)\) denotes the average centerline intensity, and \(\sigma_c\) the standard deviation of the intensity along the initial centerline. An illustration of Eq. 3.1 is shown in Fig. 3.1. Intensity fluctuations that are only slightly higher than the estimated lumen intensity
3.2. Segmentation and Quantification Method

![Image](image1.png)

Figure 3.1: An illustration of hyper-intense suppression along a profile. (a) the original image showing the profile location, (b) the intensity profile of the original image and the simulated profile after hyper-intensity suppression.

will only be marginally affected by the hyper-intensity suppression. In Fig. 3.2, we show an example of the medialness measure applied to both the original image and the hyper-intense-suppressed image. The green contour denotes the manual segmentation and the green marker points to the position with maximal medialness. The maximal medialness in which calcium has been suppressed is located more towards the lumen center for images with hyper-intense suppression.

3.2.2 Lumen Segmentation

A Geodesic Active Contour [17, 18] is commonly used to steer a level set to the lumen border which is defined by a high gradient magnitude. However, for atherosclerotic vessels, the gradient magnitude is not sufficient to find the lumen border since calcified regions adjacent to the lumen yield an even higher value of the gradient magnitude. Fig. 3.3(c) shows an example of the gradient magnitude of a carotid artery in CTA. In this case, the gradient between lumen
Chapter 3. Lumen Segmentation and Stenosis Quantification in CTA

Figure 3.2: Medialness computation with and without hyper-intense suppression. (a) original image, (b) medialness of original image, (c) hyper-intense suppressed image, (d) medialness of hyper-intense suppressed image.

Figure 3.3: Example of: (a) original CTA of atherosclerotic carotid arteries, (b) original CTA overlaid by manual segmentation (red) and segmentation using only boundary information (yellow), (c) corresponding gradient magnitude of original CTA, (d) gradient magnitude of original CTA overlaid by manual segmentation and segmentation using only boundary information.

and soft plaque tissue is weaker than the gradient between calcification and soft plaque tissue. If the level set is steered to the region with maximal gradient, it will not segment the lumen appropriately, the result will erroneously cover the plaque soft tissue region as well, as shown in Fig. 3.3(b) to Fig. 3.3(d).

To avoid this we include local lumen-intensity-based terms in the energy formulation. The foreground voxels should have an intensity as similar as possible to the lumen intensity and the background voxels should have an intensity as dissimilar as possible to the lumen intensity. Combining this with a Geodesic
Active Contour gives the following energy to be minimized:

\[ E(S) = \gamma \iint_S P(I(S(u,v)))|S'(u,v)|dudv \]

\[ + \alpha \iiint_{\Omega_1} (1 - s(x))dxdydz \]

\[ + \beta \iiint_{\Omega_2} s(x)dxdydz \].

\( u \) and \( v \) are used for parameterizing the surface \( S \), i.e. for points on the surface [18], we have \( S = (x(u,v), y(u,v), z(u,v)) \). \( \Omega_1 \) represents the region enclosed by surface \( S(u,v) \), \( \Omega_2 \) represent the region not enclosed by surface \( S(u,v) \). From top to bottom in Eq. 3.2, the first term is a geodesic active contour which integrates gradient magnitude information over the whole surface \( S(u,v) \), the second term is used for minimizing the lumen intensity dissimilarity to the foreground, and the last term is used for minimizing the lumen intensity similarity to the background. The parameters \( \alpha \) and \( \beta \) are used to weigh the boundary and regional terms. The term \( P(I(S)) \) is inversely proportional to the gradient magnitude at scale \( \sigma_g \), \( \frac{1}{|G_{\sigma_g}I|+\eta} \). \( \eta \) is a small positive value to prevent dividing by zero. \( s(x) \) determines the similarity of a voxel to the lumen:

\[ s(x) = e^{-\left(\frac{I(x) - I_m(x)}{\sigma^2}\right)^2} \].

Here \( I_m(x) \) represents the local mean intensity of the lumen, which is obtained from a spherical region \( \mathcal{S}_x \) centered at the closest point on the extracted centerline. Let \( \{x_c\} \) denote the set of points along the centerline, then \( I_m(x) \) is defined by:

\[ I_m(x) = \bar{I}(\text{argmin}_{x_c}(d(x, x_c))), \]

subject to: \( |\bar{I}(x) - \bar{I}_c| < k\sigma_c \)

where \( \bar{I}(x) \) is the average intensity over a region \( \mathcal{S}_x \) centred around \( x \). \( \mathcal{S}_x \) is empirically chosen to be a sphere with a radius of 1 mm. \( \bar{I}_c \) and \( \sigma_c \) are the mean and standard deviation of the intensity along the centerline, \( d(x_1, x_2) \) is the Euclidean distance between \( x_1 \) and \( x_2 \), and \( k \) is a constant which controls the tolerance of the constraint. The constraint prevents outlier intensities along the centerline to be used in determining the intensity term.

Due to partial volume effects, the intensity of voxels surrounding the calcium may be similar to the lumen intensity. Hence, in the cases where the calcium and the lumen are connected, the segmentation according to Eq. 3.2 will contain the voxels surrounding calcium. Fig. 3.4(a) shows the original image with the
manual segmentation overlaid in red and Fig. 3.4(b) shows the voxels which are between the minimal lumen intensity and maximal lumen intensity in blue. The voxels around calcium also have intensities lying in the range of the lumen intensity. The segmentation thus contains the voxels around calcium as it is also surrounded by a high gradient magnitude, shown in Fig. 3.4(c) and Fig. 3.4(d).

In order to exclude the voxels around calcium from the segmentation, we first label calcium voxels as follows:

$$C(x) = \begin{cases} 1, & I(x) - I_m(x) > T_c \\ 0, & \text{otherwise,} \end{cases} \quad (3.5)$$

and each voxel at $x$ has a label $CN(x)$ to indicate whether it is surrounding a calcium spot or not.

$$CN(x) = C(x) \oplus \mathcal{N}_x \quad (3.6)$$

where $T_c$ is experimentally selected. $\mathcal{N}_x$ is a cube of size $5 \times 5 \times 5$ voxels.

To exclude the voxels around calcium from the segmentation, the energy function is modified to penalize the inclusion of voxels that are surrounding the calcium.

$$E(S) = \gamma \int_S P(I(S(u,v)))|S(u,v)|dudv \quad (3.7)$$

$$+ \alpha \iiint_{\Omega_1} (1 - s(x))dxdydz$$

$$+ \beta \iiint_{\Omega_2} s(x)dxdydz$$

$$+ \delta \iiint_{\Omega_1} CN(x)dxdydz \quad .$$

Replacing $S(u,v)$ by a level set function $\phi(x)$, which is negative inside surface $S(u,v)$ and positive outside $S(u,v)$ [85] in Eq. 3.7, and replacing region $\Omega_2$ by the Heaviside function $H_{\epsilon}(\phi(x))$, region $\Omega_1$ by $1 - H_{\epsilon}(\phi(x))$, we get

$$E(\phi) = \gamma \iiint (H'_{\epsilon}(\phi(x))P(I(\phi(x)))\nabla\phi(x)| \nabla\phi(x)||$$

$$+ \alpha(1 - H_{\epsilon}(\phi(x))(1 - s(x))|\nabla\phi(x)|$$

$$+ \beta H_{\epsilon}(\phi(x))s(x)|\nabla\phi(x)|$$

$$+ \delta (1 - H_{\epsilon}(\phi(x))CN(x))|\nabla\phi(x)| \ )dxdydz \quad ,$$

in which $H_{\epsilon}(\phi(x))$ is a regularized version of the Heaviside function and $H'_{\epsilon}(\phi(x))$ is its derivative, similar to the approach by Chan et al. [22].
3.2. Segmentation and Quantification Method

Figure 3.4: (a) original image with the manual segmentation overlaid in red, (b) original image with a mask in blue indicating the voxels whose intensity is between the maximum and minimum lumen intensity, (c) the segmentation using only gradient magnitude and regional intensity (by Tang et al. [111]) shown in green, yellow is the overlap between manual segmentation and segmentation from the work in [111], (d) zoomed-in version of image in (c).

Minimizing Eq. 3.8 by gradient descent yields

\[
\phi_t = H_x(\phi(x)) \left\{ \gamma_c \kappa P(I(\phi(x))) |\nabla \phi| + \gamma_a \nabla P(I(\phi(x))) \cdot \nabla \phi - \alpha (1 - s(x)) |\nabla \phi| + \beta s(x) |\nabla \phi| - \delta CN(x) |\nabla \phi| \right\} .
\]

For tubular structure segmentation, \( \kappa \) is changed to be the minimum principal curvature [72].

There are five terms in Eq. 3.9, from top to bottom these are the curvature term for maintaining the tubular structure of the vessel, the advection term for finding the lumen border in healthy regions, the foreground regional term for maintaining intensity similarity inside the vessel, the background regional term for maintaining intensity dissimilarity in the background, and the spatial term for excluding the voxels around calcium. The advection term is bilateral and depends on the current position of the contour with regard to the gradient potential valley. The sign in front of each remaining term indicates the direction of each term during evolution, negative means shrinking while positive means expanding. In our implementation, the curvature term and advection term are weighted separately by \( \gamma_c \) and \( \gamma_a \).
3.2.3 Side Branch Removal

Side branches may occur in the distal region of the external and internal branches. The segmentation obtained from Eq. 3.7 contains part of the side branches, and that will cause inaccuracies in the stenosis quantification when the segment containing side branches is included in the reference CSA/CSD calculation. Fig. 3.5(a) shows an example with side branches. Along the centerline, we extract the curved multi-planar reformatting (CMPR) image. The surface in Fig. 3.5(a) is colored in those regions where the surface distance between the manual segmentation and the semi-automatic segmentation is over 0.5 mm. The image at the level of the side branch is shown in Fig. 3.5(c), and the corresponding segmentations are shown in red in Fig. 3.5(d) (manual: green, semi-automatic: red, overlap: yellow).

![Figure 3.5](image-url)

Figure 3.5: (a) Semi-automatic segmentation color coded by the distance to the manual segmentation, red indicates that the distance to manual segmentation is over 0.5 mm, (b) initial segmentation with side branch in green and the envelope of the maximum inscribed spheres in white, (c) original cross-section, (d) original cross-section with superimposed manual segmentation (red), and semi-automatic segmentation in green, and overlap in yellow.

We propose to remove the side branches in a three-step procedure. First, from the initial segmentation, we compute the internal and external carotid artery centerlines using a publicly available package Vessel Modeling Tool Kit (VMTK, www.urlwww.vmtk.org) [4]. Now the centerlines are also computed using a minimum cost path approach with the cost defined to be the inverse of the maximum inscribed sphere’s radius. Second, an envelope of the maximum inscribed spheres of the initial segmentation is generated using the same package. The side branches are distant to the envelope, shown in Fig. 3.5(b). However,
3.2. Segmentation and Quantification Method

Figure 3.6: (a) Manual segmentation in green and initial segmentation with side branch in transparent green; (b) initial segmentation with side branch in green and envelope in red, and overlap in yellow.

This is not sufficient to identify side branches, as in the stenotic areas, especially in cases of asymmetric stenosis, the initial segmentation is also partially distant to the envelope, c.f. in Fig. 3.6(a) and Fig. 3.6(b). Third, to detect the location of side branches we compute the long axis through cross-sections of the segmentation along the centerline. The long axis is defined to be the longest axis that divides the cross-sectional area in two equal parts. Subsequently, this long axis is smoothed along the centerline using a Gaussian kernel with a scale of 10 mm. The side branch candidate locations are the locations where the original long axis is larger than the smoothed long axis and at the same time the distance to the maximum sphere envelope exceeds a threshold. An example of a side branch candidate detection is shown in Fig. 3.7(a) and Fig. 3.7(b). The green curve is the long axis before smoothing and the red curve is the long axis after smoothing. From Fig. 3.7(a), two regions have a long axis prior to smoothing that is larger than the smoothed axis. The region on the left is the carotid bifurcation region but in that region the segmentation is not distal to the envelope of the maximum inscribed spheres. In that region the maximum distance between the envelope of maximum inscribed spheres and the contour in a cross-sectional plans along the centerline is small (shown in blue). Thus only the region on the right will be seen as a side branch. From Fig. 3.7(b), an asymmetric stenosis will have a large distance to the envelope of maximum inscribed spheres but the long axis is not larger than the smoothed long axis. Only the region that has both a larger long axis compared to smoothed long axis and a large distance to the envelope of maximum inscribed spheres will be
considered as a side branch. In this work, a distance between the envelope of maximum inscribed surface and the semi-automatic segmentation will be considered as an indication of side branch if it is over 1 mm, shown in the dash blue line in Fig. 3.7(a) and Fig. 3.7(b).

### 3.2.4 Stenosis Detection and Grading

We quantify the stenosis using the NASECT (North American Symptomatic Carotid Endarterectomy Trial) criterion [6]. The area/diameter of the stenotic segment is divided by the area/diameter of a normal, distal segment of the internal carotid artery (also called reference segment, where the vessel walls are running parallel) and subtracted from one. Although there may be multiple stenoses in one internal carotid artery, in this work, we select the most severe stenosis.

From the segmentation, we extract the internal centerline using VMTK. Along the centerline, we calculate the area and diameter of the cross-sectional plane, i.e. cross-sectional area (CSA) and cross-sectional diameter (CSD). The diameter is defined as the length of the shortest axis that splits the cross-sectional area in two equal parts. An example of the short axis calculation is shown in Fig. 3.8. We then smooth the CSA/CSD curve by a Gaussian filter with a scale of 1 mm to suppress noise. The stenotic segment is the position where the smoothed CSA/CSD is minimal. The reference segment is the segment which is 2 to 3 cm distal to the stenotic segment. The reference CSA/CSD is then the average value in the reference segment region. An example of the CSA as a function of centerline position is depicted in Fig. 3.9.

### 3.3 Experiments

#### 3.3.1 Data and Implementation

The proposed method was trained on 15 datasets and evaluated on 41 datasets of the "Carotid Lumen Segmentation and Stenosis Grading Challenge" [39]. We implemented the proposed segmentation method in ITK (www.itk.org), ignoring $H'_c(\phi(x))$ because of the narrow-band implementation ($|\phi(x)| < 3$) [132]. Narrow-band methods update only the level set evolution around the neighborhood of zero level set instead of the whole image. We implemented the stenosis quantification in VTK (www.vtk.org) and VMTK (www.vrntk.org). The centerline extraction takes on average 10 mins; the level set evolution takes on average 15 mins; the side branch removal takes around 20 mins; the stenosis quantification takes on average 5 seconds. All timings were done using a linux
3.3. Experiments

Figure 3.7: An example of side branch detection. Long axis (green), highly smoothed long axis (red) and the maximum distance between the contours in cross-sectional planes and the envelope of maximum inscribed spheres along the external centerline. (a) carotid artery with side branch, (b) carotid artery without side branch but a stenosis.

workstation with 16 processors (AMD 6172) with 12 cores each. And each processor has a clock frequency of 2.1 GHz and RAM memory of 256 GB. None of the processing used parallel implementations.
3.3.2 Parameter Optimization

The parameters that were fixed in this method are listed in Table 3.1. We optimized the segmentation method by tuning the four remaining parameters: the curvature weight $\gamma_c$, the advection weight $\gamma_a$, the foreground regional weight $\alpha$ and the threshold $T_c$ that is used in determining calcium and voxels surrounding calcium. We optimize the four aforementioned parameters for three different metrics: the Dice similarity coefficient (DSC) of the lumen segmentation [29], the CSA-based stenosis error ($SE_a$) and the CSD-based stenosis error ($SE_d$). The curvature weight $\gamma_c$ is varied from $1e-5$ to $1e1$ logarithmically in 6 steps, and we include a curvature weight of 0. The advection weight $\gamma_a$ is varied from 5 to 25 with a step size of 5, the regional weight $\alpha$ is varied from 0 to 0.09 with a step size of 0.03, and the threshold $T_c$ is varied from 60 HU to 150 HU with a step size of 15 HU. This optimization procedure examined 840 different combinations of the four parameters. The optimal parameter combination that maximizes the DSC was $\gamma_c = 1$, $\gamma_a = 20$, $\alpha = 0$ and $T_c = 120$ HU. Fig. 3.10 shows the result of the training step with regard to two out of four parameters while fixing the remaining two to their optimal values. Fig. 3.10 (c) and (d) show that the curvature weight $\gamma_c$ hardly influences the DSC between 0 and 1. As a result we fixed the curvature weight to 1 and minimize the $SE_a$ and $SE_d$ for different combinations of $\gamma_a$, $\alpha$ and $T_c$. In this stage, the three parameters have larger ranges compared to that used in maximizing DSC to make sure that the optimal value is not in the border of the parameter range. $\gamma_a$ ranges from 5 to 40 with a step size of 5, $\alpha$ ranges from 0 to 0.21 with a step size of 0.03, and $T_c$ ranges from 60 HU to 300 HU with a step size of 15 HU. Fig. 3.11 and Fig. 3.12 show the result of the stenosis quantification error as a function
Figure 3.9: An illustration of the stenosis grading. Internal CSA is to the right of common CSA. (a) A color-coded 3D surface based on the CSA curve. (b) Corresponding CSA curve.

of two out of three parameters when the third one is kept at its optimal value.

Table 3.2 lists the optimal parameters for three different optimization metrics and the performance according to all three metrics.
Chapter 3. Lumen Segmentation and Stenosis Quantification in CTA

Table 3.1: List of level set segmentation parameters (not optimized in training).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>minimum root mean square error</td>
<td>0.0001</td>
</tr>
<tr>
<td>number of iterations</td>
<td>1000</td>
</tr>
<tr>
<td>initial tube radius (mm)</td>
<td>2</td>
</tr>
<tr>
<td>Gaussian gradient scale $\sigma_g$ (mm)</td>
<td>1</td>
</tr>
<tr>
<td>$\beta$</td>
<td>1</td>
</tr>
<tr>
<td>$\delta$</td>
<td>1</td>
</tr>
<tr>
<td>$\sigma$ in Eq. 3.3 (HU)</td>
<td>90</td>
</tr>
<tr>
<td>$k$ in Eq. 3.4</td>
<td>0.5</td>
</tr>
<tr>
<td>$\mathcal{N}_x$ size</td>
<td>5x5x5</td>
</tr>
</tbody>
</table>

Table 3.2: Summary of optimal parameters for three metrics: DSC, $SE_a$, $SE_d$.

<table>
<thead>
<tr>
<th>Metrics</th>
<th>optimal value</th>
<th>$\gamma_c$</th>
<th>$\gamma_a$</th>
<th>$\alpha$</th>
<th>$T_c$ (HU)</th>
<th>$SE_a$ (HU)</th>
<th>$SE_d$ (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSC</td>
<td>91.5%</td>
<td>1</td>
<td>20</td>
<td>0</td>
<td>120</td>
<td>91.5%</td>
<td>19.7%</td>
</tr>
<tr>
<td>$SE_a$</td>
<td>17.1%</td>
<td>1</td>
<td>5</td>
<td>0.15</td>
<td>225</td>
<td>91.0%</td>
<td>17.1%</td>
</tr>
<tr>
<td>$SE_d$</td>
<td>11.3%</td>
<td>1</td>
<td>5</td>
<td>0.03</td>
<td>180</td>
<td>90.4%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

Figure 3.10: Lumen segmentation accuracy expressed in DSC for various combinations of parameters on the training set. From top left to bottom right, segmentation accuracy (a) as a function of $T_c$ and $\alpha$ at $\gamma_c = 1$ and $\gamma_a = 20$, (b) as a function of $\gamma_c$ and $\gamma_a$ at $T_c = 120$ HU and $\alpha = 0$, (c) as a function of $\gamma_c$ and $\alpha$ at $T_c = 120$ HU and $\gamma_a = 20$, (d) as a function of $\gamma_a$ and $T_c$ at $\alpha = 0$ and $\gamma_c = 1$, (e) as a function of $\alpha$ and $\gamma_a$ at $\gamma_c = 1$ and $T_c = 120$ HU, (f) as a function of $\gamma_c$ and $T_c$ at $\gamma_a = 20$ and $\alpha = 0$. 
3.3. Experiments

Figure 3.11: Cross-sectional area-based stenosis quantification for various combinations of parameters on the training set. From top left to bottom right, $SE_a$ (a) as a function of $T_c$ and $\alpha$ at $\gamma_a = 5$, (b) as a function of $\gamma_a$ and $T_c$ at $\alpha = 0.15$, (c) as a function of $\alpha$ and $\gamma_a$ at $T_c = 225$ HU.

Figure 3.12: Cross-sectional diameter-based stenosis quantification for various combinations of parameters on the training set. From top left to bottom right, $SE_d$ (a) as a function of $T_c$ and $\alpha$ at $\gamma_a = 5$, (b) as a function of $\gamma_a$ and $T_c$ at $\alpha = 0.03$, (c) as a function of $\alpha$ and $\gamma_a$ at $T_c = 180$ HU.
### 3.3.3 Segmentation Results

On 41 carotid arteries of the testing set, the proposed method successfully segmented 38 carotid arteries. Three cases failed due to erroneously extracted centerlines. Table 3.3 lists our segmentation accuracy. The average DSC obtained with the parameters trained by maximizing DSC is 89.3 %, and the average mean surface distance (MSD) is 0.38 mm. The average DSC obtained with parameters trained by minimizing $SE_a$ is 90.2 %, and the average mean surface distance (MSD) is 0.34 mm. The average DSC obtained with the parameters trained by minimizing $SE_d$ is 88.9 %, and the average mean surface distance (MSD) is 0.43 mm. We performed a paired t-test to check for statistical significance of the aforementioned difference, also with our previous work [111]. Since for the challenge data, individual stenosis grades are not available to the participants, we could only perform this analysis for the segmentation results. The results of the paired t-test are listed in Table 3.4. The segmentation obtained with the parameters trained by minimizing $SE_a$ performs statistically significantly better than the three other segmentation results. In the challenge website, it is possible to compare each testing result with the published methods. We compared the best segmentation that we obtained (SegMin$SE_a$) to the three method that ranked first (Gülsün [38]), second (Krissian [62]) and third (Hui Tang [111]). SegMin$SE_a$ ranks second in the segmentation challenge.

After applying the side branch removal step, the side branches are successfully removed, shown in Fig. 3.13(a) and Fig. 3.13(b). Example results of the proposed segmentation method obtained at parameters trained to maximize DSC are shown in Fig. 3.14(a) to Fig. 3.14(f). In all cases, the plaque tissue is not included in the segmented lumen. With the $CN$ term in the energy function of Eq. 3.8, the voxels around calcium are also excluded from the segmentation.
Table 3.4: Paired t-test of segmentation performance between Hui Tang et al. [111] (SegHT), segmentation with the parameters trained by maximizing DSC (SegMaxDSC), segmentation with the parameters trained by minimizing $SE_a$ (SegMin$SE_a$), segmentation with the parameters trained by minimizing $SE_d$ (SegMin$SE_d$), Confidence Interval = 95%.

<table>
<thead>
<tr>
<th></th>
<th>SegHT</th>
<th>SegMaxDSC</th>
<th>SegMin$SE_a$</th>
<th>SegMin$SE_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SegHT</td>
<td>–</td>
<td>0.449</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SegMaxDSC</td>
<td>–</td>
<td>–</td>
<td>0.006</td>
<td>0.925</td>
</tr>
<tr>
<td>SegMin$SE_a$</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.000</td>
</tr>
<tr>
<td>SegMin$SE_d$</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Figure 3.13: Example of the side branch removal

### 3.3.4 Stenosis Quantification Results

We tested three sets of parameters for the stenosis quantification trained using the three metrics: DSC, $SE_a$ and $SE_d$. The results are listed in Table 3.5. Before our submission, the MARACAS method performed the best in the stenosis challenge among the three previously submitted stenosis quantification results. As a result, this table only compares our testing results with the MARACAS method. We compared the best quantification that we obtained (MinAreaStenosis) to the the method that ranked first (MARACAS [135]). MinAreaStenosis ranks first in the stenosis quantification challenge.

### 3.3.5 Reproducibility with respect to user interaction

We also investigated the reproducibility of the method in view of the minimal user action (selecting 3 seed points) required. We automatically apply a random
Figure 3.14: Segmentation example for an atherosclerotic vessel with optimized parameters obtained at max DSC (\( T_c = 120 \) HU and \( \alpha = 0 \) at \( \gamma_c = 1 \) and \( \gamma_a = 20 \)), manual (green), semi-automatic method (red), overlap (yellow). (a), (b), (c) semi-automatic segmentation without the term for excluding voxels around calcium. (d), (e), (f) semi-automatic segmentation with the term for excluding voxels around calcium.

Table 3.5: Averages stenosis

<table>
<thead>
<tr>
<th>Team name</th>
<th>Total success</th>
<th>( SE_\alpha ) %</th>
<th>( SE_\delta ) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>41</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ObserverA</td>
<td>41</td>
<td>3.4</td>
<td>2.9</td>
</tr>
<tr>
<td>ObserverB</td>
<td>41</td>
<td>5.4</td>
<td>4.3</td>
</tr>
<tr>
<td>ObserverC</td>
<td>41</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td>MinAreaStenosis</td>
<td>41</td>
<td>19.2</td>
<td>15.7</td>
</tr>
<tr>
<td>MaxDSCStenosis</td>
<td>41</td>
<td>22.8</td>
<td>16.8</td>
</tr>
<tr>
<td>MARACAS [135]</td>
<td>41</td>
<td>17.0</td>
<td>16.9</td>
</tr>
<tr>
<td>MinDiamStenosis</td>
<td>41</td>
<td>24</td>
<td>18.7</td>
</tr>
</tbody>
</table>

3D translation to the original seed points to simulate the inter-observer variability of seed points clicking. The translation is uniformly distributed between the range of \([-r/4, r/4]\), where \( r \) is the normal radius of the common, internal and external original seeds. In our experiment, \( r \) is 4.0 mm in the common, 2.0 mm in the internal and 1.5 mm in the external carotid artery.
3.4 Discussion and Conclusion

Table 3.6: Comparison of the segmentation and quantification results obtained with the original seeds and automatically shifted seeds (paired t-test Confidence Interval = 95%)

<table>
<thead>
<tr>
<th></th>
<th>DSC %</th>
<th>SEa %</th>
<th>SEd %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original seeds</td>
<td>91.5</td>
<td>17.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Translated seeds</td>
<td>91.4</td>
<td>17.2</td>
<td>12.1</td>
</tr>
<tr>
<td>Mean absolute difference</td>
<td>0.7</td>
<td>4.9</td>
<td>2.7</td>
</tr>
<tr>
<td>p value</td>
<td>0.67</td>
<td>0.98</td>
<td>0.48</td>
</tr>
</tbody>
</table>

We performed centerline extraction, segmentation and stenosis quantification with the repositioned seeds on 15 training data sets. Reproducibility w.r.t seed point position was assessed by comparing the DSC and stenosis quantification error obtained with the original seed points and the automatically shifted seed points. The results are shown in Table 3.6.

The DSC was calculated while using the parameters obtained by maximizing the DSC on the training set, the SEa (SEd) was calculated while using the parameters obtained by minimizing SEa (SEd) on the training set. The parameters are provided in Table 3.2.

The paired t-test shows that, for the segmentation results and the quantification results, there is no significant difference between the ones obtained with the original seed points and with the translated seed points, which indicates that our method is robust w.r.t seed point position selection as long as the seed points are within the range of [-r/4, r/4] apart from the original seed points.

3.4 Discussion and Conclusion

We developed and quantitatively validated a semi-automatic level set based method for carotid artery segmentation and subsequent stenosis quantification.

The segmentation method was trained on 15 carotid arteries. In the training stage three different metrics were optimized: the Dice similarity coefficient of the segmented lumen, and stenosis degree, either measured based on cross-sectional diameters or cross-sectional areas.

When optimizing parameters using the Dice similarity coefficient as metric, it was found that the optimal value of the foreground regional weight is zero. The foreground regional term provides a shrinking force during the level set evolution. Probably, since our segmentation is initialized by a centerline inside the carotid arteries, a shrinking force is not required. The optimal threshold to define the calcium is 120 HU, which indicates that on average calcified objects are at least 120 HU higher than the nearby lumen intensity.
The method with optimized parameters was evaluated on 41 carotid arteries. The Dice similarity coefficient obtained with the parameters optimized by training on minimizing the cross-sectional area-based stenosis is slightly higher than that obtained at parameters trained maximizing the Dice similarity coefficient. Whereas the difference is small, it is statistically significant ($p = 0.006$). The stenosis error on the testing set is the smallest for the optimal parameter values obtained by minimizing cross-sectional area-based stenosis. The test results obtained by training on minimizing cross-sectional diameter-based stenosis are worse than when training using the other metrics. Also, the optimization landscapes for the parameter optimization for the cross-sectional diameter-based stenosis were not as smooth as those for the other metrics. This demonstrates that optimizing using a more stable surrogate metric, such as Dice similarity coefficient or area-based stenosis give better results in our quantitative results. Furthermore, the better performance also for Dice using the optimal parameters from the training on area-based stenoses suggests that it may be good to use a training set size larger than the one provided by the challenge.

Compared to the other carotid segmentation and quantification methods submitted to the same challenge, we obtained a slightly lower Dice similarity coefficient compared to Gülsün et al. [38] who ranked first. Compared to our own previous work [111] which does not address voxels around calcium and a removal of side branches, the proposed method improved the average Dice similarity coefficient from 88.9% to 90.2%. In other words, it reduced the missegmentation from 11.1% to 9.8%. However, the impact in individual datasets can be considerably larger, since calcified objects and side branches do not occur in all datasets.

Overall, our proposed method ranks first in the carotid artery challenge w.r.t carotid artery stenosis quantification, slightly higher than the MARACAS algorithm in the current challenge ranking system. The challenge setup, however, did not allow us to test whether the difference between methods is significant.

In our evaluation we found that our method may detect stenoses in vessels with slightly varying diameter, which are considered to be healthy. Since this results only in a minor stenosis, which is not clinically relevant, this does not pose an issue when using the method in practice.

In the future, we intend to use our approach for the stenosis grading in clinical studies, e.g. by investigating the relation of stenosis grade with clinical events. Additionally, our approach could be used in clinical practice by presenting the segmentation results and also the minimal area curves, allowing the physician to manually select the minimal area location and the reference segment.

In conclusion, we proposed an automated carotid lumen segmentation and stenosis quantification method which is able to exclude plaque tissues, voxels
around calcified objects and side branches from the segmentation, and evaluated this method in the context of a public challenge. We show that different parameter settings are optimal for carotid lumen segmentation than for carotid artery stenosis quantification. With respect to lumen segmentation accuracy our method ranks second in the carotid artery challenge, and with respect to carotid artery stenosis quantification it is the best performing method that has submitted results.
Chapter 3. Lumen Segmentation and Stenosis Quantification in CTA
Chapter 4

Segmentation and Volume Quantification of Intra-plaque Hemorrhage in T1w-MRI

Intra-plaque hemorrhage (IPH) is associated with plaque instability. Therefore the presence and volume of IPH in carotid arteries may be relevant to predict the progression of atherosclerotic disease and clinical events. A semi-automatic method for segmentation and volume quantification of IPH has been developed and evaluated. The method only requires minimal user interaction, i.e. a few mouse clicks inside the hemorrhage. The semi-automatic segmentation method models the intensity of the IPH and the background in T1-weighted MRI to be smoothly varying. Segmentation is performed with a piecewise-smooth regional level set method, which is initialized by user-clicked seed points. The parameters of this method are optimized using a leave-one-out strategy by maximizing the Dice similarity coefficient (DSC) between manual and semi-automatic segmentations. We evaluated the IPH segmentation method on 22 carotid arteries and obtained an overall DSC of 0.52 between manual and semi-automatic segmentations. In 10 carotid arteries, two observer segmentations are available. The inter-observer DSC is 0.57, which is comparable to the DSC of the method (0.55) on this data. The correlation between the IPH volumes extracted from our segmentation and the manual segmentation is 0.88, which is close to the inter-observer volume correlation of 0.92. Twelve out of 22 carotid arteries are scanned twice with a time interval of less than two weeks; these data sets are

This chapter is based on:
used for evaluation of the reproducibility of the method. The correlation between the IPH volumes obtained after semi-automatic segmentation of the first and the second scan is 0.97. We also evaluated the robustness w.r.t. the manual initialization by manually clicking two sets of seed points in these 12 carotid artery pairs. The correlation between the two volumes obtained from the two sets of seed points is 0.99. We show that semi-automatic segmentation and quantification of intra-plaque hemorrhages is feasible with an accuracy in the range of the inter-observer variability. The method has excellent reproducibility w.r.t. rescanning and manual initialization.
4.1 Introduction

Atherosclerosis is one of the main underlying causes of cardiovascular events such as ischemic stroke, and a major cause of mortality and morbidity [31]. Atherosclerosis progresses with age and remains asymptomatic prior to clinical events [31]. Many studies investigated the relation between plaque growth and various other factors, such as vessel geometry and plaque composition [21, 115, 107]. Recently, intra-plaque hemorrhage (IPH) was found to be associated with the increase in size of the necrotic core and lesion instability in coronary plaques [60] and therefore, IPH is considered as a high risk component of the vulnerable plaques [99]. IPH was also reported to be related to (recurrent) neurological events during follow-up [2]. Takaya et al. [109] found that the presence of IPH in carotid atherosclerotic plaques accelerated plaque progression over an 18-month period. The association between the size of IPH and plaque progression has not been investigated previously. MRI can be used for visualizing IPH [130]. It has been shown that high resolution MR has excellent capabilities for differentiating IPH from other carotid plaque tissues [15, 10]. To study the association between IPH size and plaque progression, an MRI study was designed as part of a population-based study [46]. Purpose of our work is to develop a method for the precise and robust quantification of IPH volume from magnetic resonance imaging (MRI) data, and evaluate it on those data.

Manual quantification of IPH (or other plaque characteristics) is a tedious procedure, prone to inter- and intra-observer variability. Therefore, there is a large interest in automated procedures for plaque assessment. Pattern recognition and machine learning methods play an important role in (semi-) automatic segmentation of plaque components [71, 47, 122]. Hofman et al. [47] quantified the relative area of all detected atherosclerotic plaque components, including IPH, using supervised classification techniques. Their method needs manual annotation of the inner and outer vessel wall to obtain a mask of the plaque and thus requires a significant amount of user interaction. Liu et al. [71] segmented plaque components based on morphology enhanced probability maps from in vivo MRI, but IPH is not included in their work. Van Engelen et al. [122] segmented the plaque composition in ex vivo MRI using a machine learning method. Similar to the work by Hofman et al. [47] and Liu et al. [71], this method requires manual annotation of the inner and outer vessel wall.

In this chapter, we present a semi-automatic approach to quantify the carotid IPH volume using manually selected seed points. The seed points are used to initialize a piecewise-smooth regional level set method that segments the IPH. Our main contributions are: 1) we demonstrate the feasibility of precise IPH segmentation without vessel wall annotation; 2) we perform an extensive validation study to investigate the accuracy, and inter-scan reproducibility and
robustness of the proposed semi-automatic IPH segmentation approach.

4.2 Materials and Methods

4.2.1 Materials

**Data Description** The data in this work is obtained from a prospective cohort study to investigate the prevalence, incidence, and risk factors of chronic diseases in an asymptomatic group of elderly aged 45 years and older [46]. In this study, 1006 participants with a vessel wall thickness larger than 2.5 mm at plaque locations (determined by 2D ultrasound) underwent MR imaging of the carotid arteries [121]. The study procedures and consent forms were reviewed and approved by The Medical Ethics Committee of the Erasmus Medical Center.

From this data set we randomly selected 52 T1-weighted (Tlw) MRI images (see Fig. 4.1) of 40 carotid arteries from 27 subjects among the participants who contain IPH. The 52 images were further divided in subsets, denoted by A, B, C1 and C2, based on the availability of manual reference data, and re-scan data. Set A consists of 18 carotid arteries from 12 subjects with a consensus annotation by two observers. This set is used for parameter optimization. Ten data sets (Set B) from 6 subjects have intra- / inter-observer annotations, and for 12 carotid arteries we have images at two time points (C1 and C2), with less than 2 weeks between the acquisitions. The accuracy of the proposed method was evaluated using Set B and C1 (22 data sets). The reproducibility and robustness of the method was evaluated on the 12 carotid arteries (24 image data sets) from 10 subjects for which two images are available (C1 and C2) and for which two observers provided seed points. An overview of the data used in this chapter is shown in Fig. 4.1.

All scans were obtained with a 1.5-T scanner (GE Signa Excite II; GE Healthcare, Milwaukee, WI, USA) with a bilateral phased-array surface coil. The MRI acquisition parameters for the T1w MRI scans are as follows: a 3D Gradient Recalled Echo sequence, scanned in the coronal plane, parallel to the common carotid artery, repetition time / echo time: 15.7 / 1.8 ms, field of view (FOV): 18 x 18 cm², matrix size: 192 x 180 in the coronal plane. The slice thickness is 1.0 mm and the flip angle is 40°. The stenosis is measured manually using the NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria [6] and ranges from 0 % to 90 % (23 % on average). All scans were reviewed by two independent physicians, both with two years experience in reading MRI, under supervision of a neuro-radiologist with more than 8 years of experience in MRI plaque analysis.
4.2. Materials and Methods

52 T1W MRI images from the Rotterdam Study

- Testing
- Training

Consensus (18 images) Set A

Inter/intra-observer Variability (10 images) Set B

Reproducibility & Robustness (12 images + 12 images) For two time points Set C1 and C2

Figure 4.1: Description of image data

Figure 4.2: An example of a manually drawn contour and the partial volume image generated from the manual contour

Reference standard The IPHs were manually annotated in axial slices using in-house developed software. Observers are able to zoom in and out and delineate the border by drawing contours around the IPHs per slice. For Set A, two readers, R1 and R2, annotated the IPH border in consensus, yielding annotation $O^A_{consensus}$. For Set B, reader R1 performed the annotation two times, resulting in two annotations labeled as $O^B_{11}$ and $O^B_{12}$, which enable the assessment of the intra-observer variability. The time interval between the two annotations is over 2 months. Reader R2 performed the annotation once, resulting in one annotation labeled as $O^B_2$ to allow assessments of the inter-observer variability. Reader R1 also annotated set C1 and C2 twice. The manual contours were used to create a partial volume image by calculating the fraction of the voxel inside the contour (a polygon) for every voxel in each slice. In the partial volume image, the intensity value ranges between 0 and 1, indicating the fraction of each voxel occupied by the IPH (Fig. 4.2).
Chapter 4. Segmentation and Volume Quantification of Intra-plaque Hemorrhage in T1w-MRI

4.2.2 Methods

The IPH segmentation is performed by a piecewise regional level set initialized by seed points. A region of interest is automatically generated around the seed points. The size of the region is defined by a box whose size is 15 voxels larger in all directions than the smallest bounding box that encloses all seed points. Fig. 4.3 shows a slice through the 3D volume, the projected seed points and the automatically cropped image.

For the semi-automatic IPH segmentation we require a method that can deal with: 1) varying size of IPHs, 2) intensity variation within the IPH due to variations in plaque composition, and 3) intra-scan intensity variations. Based on these requirements, we chose a piecewise-smooth regional level set for this purpose [69]. The level set’s energy function is

$$E_{RSF}(\phi(x)) = \lambda_1 \int \int K_\sigma(y - x)(I(y) - f_1(x))$$

$$H_1(\phi(x))dxdy$$

$$+\lambda_2 \int \int K_\sigma(y - x)(I(y) - f_2(x))$$

$$H_2(\phi(x))dxdy$$

$$+v|\nabla \phi(x)|,$$

where $\phi(x)$ is a signed distance map which is negative inside the segmentation surface $S$, positive outside and zero at the border. $H_1(\phi(x))$ is the Heaviside function representing the current segmentation during each iteration which has the value 0 inside the surface $S$ and 1 outside, and $H_2(\phi(x))$ is equal to 1 - $H_1(\phi(x))$. $K_\sigma(y - x)$ is a Gaussian function which controls the size of a spherical region in which the intensity inhomogeneity is ignored, a larger (smaller) scale $\sigma$ indicates an assumption of homogenous intensity in a larger (smaller) local region and thus a less (more) severe intensity inhomogeneity. The term $f_1(x)$
(i = 1, 2) denotes the estimated mean intensity as a function of image location. We use a local estimate \( f_i(x) \) instead of a global constant to estimate the mean intensity in the fore-and background, in order to take intensity inhomogeneity into account. Li et al. used a standard gradient descent method to minimize Eq. 4.1, which upon convergence yields the final segmentation \( \phi(x) = 0 \). In each iteration, we need to update \( f_i(x) \), \( i = 1, 2 \) according to

\[
f_i(x) = \frac{K_\sigma(x) \ast [H_i(\phi(x))I(x)]}{K_\sigma(x) \ast H_i(\phi(x))}, \quad i = 1, 2
\]

where \( \ast \) denotes the convolution operation. A curvature term, weighted by \( v \), is included to enforce the smoothness of the surface [19].

### 4.3 Experiments and Results

Experiments are designed to determine both inter- and intra-observer variability, and to determine the difference between the semi-automatic method and the observers. First, inter- and intra-observer variability are assessed. Subsequently, for the semi-automatic method, parameter settings for IPH segmentation are optimized on training set \( A \). Then, the segmentation results are compared with the manual reference standard. This value is further compared with the inter- / intra-variability. Finally, the robustness and inter-scan reproducibility of the method is investigated.

#### 4.3.1 Inter- and Intra-observer Variability

The inter-observer Dice Similarity Coefficient (DSC) [29] is defined as the average of the two DSC's between the first observer's and the second observer's annotations, and is found to be 0.57. The intra-observer DSC is defined as the DSC between the two annotations of the first observer, and is equal to 0.62. Fig. 4.4 shows the scatter plot of volume quantifications from these annotations. The intra-observer correlation of volume is 0.92, while the average correlation of the inter-observer correlation of volume is 0.95.

#### 4.3.2 Parameter Optimization

The semi-automatic segmentation method includes a number of parameters: the parameter \( \lambda_1 \) and \( \lambda_2 \) determine the weights of the internal and external intensity dissimilarity; \( v \) determines the weight of the curvature which controls the smoothness of the segmentation, and \( \sigma \) is the scale of the Gaussian function.
which controls the size of the region. The optimal value for these parameters was determined in a leave-one-out fashion on data set A. Since only the relative value of the internal and external weights, $\lambda_1$ and $\lambda_2$, and curvature weight $v$ matters, we fixed $\lambda_2$ to be 1 and optimized the values for $\lambda_1$ and $v$, as well as the parameter $\sigma$. The curvature weight $v$ was trained from 0.001 - 0.007 in 7 steps. The internal weight $\lambda_1$ was varied from 0.9 - 1.8 with a step size of 0.1. The Gaussian kernel scale $\sigma$ was varied between 0.1 and 1 in two steps. We fixed the number of iterations to 200. The initial size of the segmentation is a sphere with a radius of 1 mm around the seed points. The leave-one-subject-out training results are shown in Table 1. The overall optimal values for IPH segmentation using the piecewise-smooth regional level set are $\lambda_1 = 1$, $v = 0.007$ and $\sigma = 0.1$ mm.

4.3.3 Accuracy

Three IPH segmentation results on the test set ($B$ and $C_1$ ) are shown in Fig 4.5. We compared the automatically quantified volume to the average volume from three annotations in Set B (10 images) and the only annotation in Set $C_1$ (12 images); both are depicted by triangles in Fig. 4.6. We obtained a DSC of 0.53 with regard to the average manual volume in Set B and the first observer in Set $C_1$. The Pearson correlation coefficient between the manual and semi-automatic volumes is 0.88. Fig. 4.6(a) also shows the scatter plot of the semi-automatic volume and the three annotations in Set B. The difference between the annotations increases with volume.

We compared our semi-automatic segmentation results for data sets $B$ to the
Table 4.1: The results after parameter training, where the second row lists the average DSC on the training set, i.e. all subjects excluding the subject in the column. The sixth and seventh rows show the DSC of the subject in the current column (test set) using these optimal parameter values. An entry listing the '-' sign indicates that the corresponding carotid artery does not have any IPHs. A DSC of '0' means that the semi-automatic segmentation method shrinks to a size of zero volume. DSC$_L$ (DSC$_R$): DSC between the manual and the semi-automatic segmentation for the left (right) carotid artery.

![Image 1](image1.png)

Figure 4.5: IPH segmentation results; the manual segmentation in green and the semi-automatic segmentation in red, (a) Dice = 0.74, (b) Dice = 0.60, (c) Dice = 0.52

inter- and intra-observer variability. The average DSC between the semi-automatic method and the average of three annotations is 0.55, which is close
Chapter 4. Segmentation and Volume Quantification of Intra-plaque Hemorrhage in T1w-MRI

4.3.4 Inter-scan Reproducibility and Robustness

Reproducibility and robustness of the method with regard to rescanning and seed point selection was assessed by applying the method to the carotid arteries in Set C1 and C2. The Pearson correlation coefficient between the 12 pairs of volumes obtained with the semi-automatic segmentation for images acquired at two time points is 0.97, which is considerably higher than that between the manual annotation of two time points (0.71). The Bland & Altman plot in Fig. 4.7 shows that the absolute difference between the two volumes increases with the average size of the IPH. We performed a paired t-test between the 12 pairs of volumes obtained with the semi-automatic segmentation acquired at two different time points, the p value is 0.250 at a confidence level of 95%, indicating a good reproducibility of the imaging techniques and semi-automatic segmentation methods. The mean absolute difference between the volumes of the first and second scan obtained from the semi-automatic segmentation is 30.7 μl whereas the mean absolute difference between the volumes of the first and the follow-up scans obtained from the manual segmentation is 80.0 μl. Fig. 4.8 shows the scatter plot of the 12 pairs of manual volumes, and the Bland & Altman plot.

We also studied the robustness of the method with respect to manual seed point selection on Set C1 and C2. Two observers independently selected two series of seed points with a time interval of more than one month. The Pearson correlation coefficient between volumes from two semi-automatic segmentations is 0.99, as seen in Fig. 4.9(a). We also performed a paired t-test between the 24...
4.4 Discussion and Conclusion

We presented a semi-automatic IPH segmentation and quantification method that does neither require manual annotation of the inner or outer vessel wall nor preprocessing to correct for intensity inhomogeneities. The method segments IPHs using a piecewise smooth regional level set initialized by a set of manually clicked seed points. We trained the parameters of this segmentation using a leaving-one-out strategy on 18 images. The method is evaluated for accuracy on 34 images, and for robustness and inter-scan reproducibility on 24 images.
We obtained a volume correlation of 0.88 between the semi-automatic segmentation and the manual segmentation in 10 data sets, which is slightly less than the inter-observer correlation. A robustness study w.r.t. the selection of seed points yielded a high volume correlation between the volumes obtained using two different seed points, which is better than the intra-observer correlation (0.92). The inter-scan reproducibility experiments showed that the segmented volumes of the semi-automatic method have a much higher reproducibility than those of the observers.

This study demonstrates that the manual annotation of IPH is subject to large observer variability. Therefore the semi-automatic results can at best also have a moderate agreement with the manual reference standard. However the robustness and inter-scan reproducibility of the semi-automatic method is better than the manual observations. This suggests that semi-automatic IPH volume quantification is to be preferred in clinical studies.

This work has some limitations. We did not evaluate the robustness of the method w.r.t. scanner type. However, as there is a parameter training part involved, we expect that similar results can be obtained on different scanners, provided that a similar parameter training experiment with representative data from that scanner is performed.

We presented a semi-automatic IPH segmentation method, which gives IPH volume quantifications with an accuracy similar to manual annotation. In the robustness study as well as the reproducibility study, the quantifications obtained with the semi-automatic method are shown to be more robust and reproducible than those obtained from manual annotations. We thus demonstrated the feasibility of semi-automatic quantification of IPH volumes.
Chapter 5

Evaluation of Semi-automatic CTA Carotid Stenosis Quantification in Patients with TIA or Minor Stroke

This chapter evaluates an automated method for carotid artery stenosis quantification in 404 carotid arteries of patients with TIA or minor stroke using CTA. First, the carotid arteries are segmented using a method requiring three manually selected seed points for initialization. Subsequently, the minimal and reference diameter are detected and measured, from which the stenosis degree is computed and the stenosis category is determined. These are then compared with the reference values obtained from manual scoring. The method successfully segments 363 out of 404 carotid arteries. It achieves a correlation of respectively 0.66 and 0.69 with the manually measured minimal and reference diameter respectively. The mean absolute error in stenosis degree between the manual and automatic method is 11.25%. The automatically assigned stenosis category agrees in 308 out of 363 carotid arteries with the manual scoring. For detecting stenosis with a degree >50%, we obtained a $\kappa$ of 0.04, a ppv of 0.32, a sensitivity of 0.90, and specificity = 0.95. The mean difference in degree of stenosis between manual stenosis quantification in DSA and the automatic CTA-based method is 22.20%. This value should be interpreted taking into account a mean difference in stenosis grade between manual stenosis quantification in DSA and CTA of 14.69%.

This chapter is based on:
Chapter 5. Evaluation of Semi-automatic CTA Carotid Stenosis
Quantification in Patients with TIA or Minor Stroke

The results indicate that whereas the evaluated generally agrees well with observers in quantifying the minimal and reference diameter, there is limited agreement when categorizing severe stenosis (9 out of 28 positives were detected).
5.1 Introduction

Carotid artery stenosis degree is an important quantitative biomarker for assessing the severity of carotid artery atherosclerosis and for therapy planning. The value of digital subtraction angiography (DSA) based stenosis degree assessment has been investigated in large randomized trials [6, 129, 90]. However, being an invasive imaging technique, DSA is associated with additional risk to the patient. Therefore, there is increasing interest in less invasive diagnosis strategies, including MRA, US and CTA. CTA has already been shown to have the ability to replace DSA in providing an accurate and fast diagnosis in patients suspected of a symptomatic carotid artery stenosis [59, 128, 84, 53].

Manual stenosis quantification in CTA is a laborious procedure and because of this, the stenosis degree is generally determined semi-quantitatively (categorized). Furthermore, manual stenosis quantification is prone to inter- and intra-observer variability [97]. Automatic algorithms have the potential to overcome these limitations, and to perform stenosis degree quantification in a standardized way. Recently, several automatic algorithms have been developed for carotid artery stenosis quantification [135, 133, 118, 111, 112].

For automated stenosis quantification to be accepted in (clinical) studies and clinical practice, the performance of the method must be thoroughly evaluated. For this purpose, a standardized evaluation framework [40] has been designed, based on 56 manually annotated CTA datasets acquired at multiple centers and with scanners of different vendors. The aim of this standardized evaluation methodology is to enable objective comparison of methods on the same data with the same metrics.

In previous work we presented a carotid artery segmentation method, and evaluated it with this framework, obtaining an average stenosis quantification error of 19.2% [112]. Further evaluation of the method is warranted for two reasons: 1) the challenge only compares manual and automatic stenosis degree, but in clinical practice, stenosis detection is also a relevant step; 2) the challenge consists of only 56 carotid arteries which have been selected without clear inclusion criteria. To enable assessment of the accuracy and robustness of the method in clinical practice a larger set of carotid arteries, representative of patient inclusion in clinical practice, is required.

In this chapter, we therefore evaluate the semi-automatic stenosis quantification method by Tang et al. [112] on a large dataset from consecutive patients with amaurosis fugax, transient ischemic attack (TIA) or minor ischemic stroke. In the evaluation, next to assessing accuracy in estimating the degree of stenosis, we investigate the performance of stenosis detection and diameter quantification of the minimal and reference diameter.
5.2 Materials and Methods

5.2.1 Materials

Data Description

Our study included patients with amaurosis fugax, TIA or minor stroke that participated in a prospective diagnostic study over two years and three months [79]. The prospective study was approved by the Institutional Review Board, and all patients gave written informed consent. CTA of the patients was performed on a Siemens 16-row MDCT scanner. Images were reconstructed with a slice thickness of 1 mm, a reconstruction interval of 0.6 mm, a FOV of 100 mm and a medium smooth convolution kernel (B30f). DSA was performed in 39 patients using an Integris V3000 angiographic unit (Philips Medical Systems, Best, the Netherlands).

The prospective study includes 351 patients, whose data were anonymized before processing. The inclusion criteria were: symptoms of carotid artery disease in the preceding 6 month (amaurosis fugax, TIA or minor ischemic stroke with a ranking score ≥ 3 and age ≥ 18 years). Exclusion criteria were: contraindication for iodinated intra-venous contrast material which includes impaired renal function (creatinin > 150 mmol/l), allergy for iodinated contrast material, thyroid carcinoma, pregnancy, and no informed consent [17]. From the 351 patients, the ones who were willing to undergo a second scan were selected for the automatic quantification. Seed points, required for the automated quantification, were clicked for the symptomatic carotid arteries. Eventually, this resulted in 205 left and 199 right carotid arteries (in total 404 carotid arteries, Set CTA-A) for quantification. In 117 left and 119 right carotid arteries (in total 236 carotid arteries) the minimal and reference diameter were manually quantified from which the stenosis degree was computed. The remaining carotids are either healthy or completely occluded, i.e. having a stenosis degree of 0% or 100%. 55 out of 119 left and 53 out of 117 right carotid arteries have a reference diameter smaller than the minimal diameter, which would indicate a ”negative” stenosis degree. These we consider as having no stenosis and the stenosis degree is thus set to be 0%. The remaining 64 left and 64 right carotid arteries (128 carotid arteries, Set CTA-B) have a stenosis degree in the range of 0 - 100%. The CTA dataset used in our study is visualized in Fig. 5.1(a).

In our dataset, 57 patients were also scanned using DSA; for 28 carotid arteries of this set seed points in CTA were available; these cases are referred to as Set DSA. All the carotid arteries in this dataset thus have manual stenosis quantification both in CTA and DSA. The DSA data description is shown in Fig. 5.1(b).
5.2. Materials and Methods

Figure 5.1: Data description of (a) CTA data and (b) DSA data.

Reference Standard

There are two types of manual reference data, viz. quantitative stenosis grading based on manual assessment of minimal and reference diameter, and semi-quantitative stenosis classification in six categories, i.e. 0%, 0-29%, 30-49%, 50-69% and 70-100%, 100%.

The quantitative manual scoring is performed by measuring the diameter at
Figure 5.2: Illustration of the lumen segmentation method. (a) Step 1: centerline extraction based on manually selected seed points. (b) Step 2, surface evolution

the location of maximal narrowing and in a distal reference segment. These measurements are performed on multi-planar reformatted images, which are parallel to the centerline of the carotid artery. One reader performed these measurements three times and calculated the average to increase the accuracy of manual quantification. The stenosis grade is measured according to the North American Symptomatic Carotid Endarterectomy (NASCET) criteria [6]. For the healthy or completely occluded carotids we set the stenosis degree to 0% and 100% respectively. The stenosis quantification in DSA is performed once using calipers.

The semi-quantitative manual stenosis grading assigns a carotid artery stenosis to one of six categories: 0%, 0-29%, 30-49%, 50-69% or 79-100%, 100% based on a qualitative assessment (236 carotids; Set CTA-B). For the healthy (stenosis degree = 0%) or fully occluded cases (stenosis degree = 100%), the stenosis category is determined. All the 404 carotid arteries have a semi-quantitative stenosis grading.

5.2.2 Method

The automatic stenosis degree quantification is based on a semi-automatic segmented lumen.

Lumen Segmentation Method

Lumen segmentation consists of two steps, depicted in Fig. 5.2. In the first step, the centerline of the carotid artery is extracted using an iterative minimum cost
5.2. Materials and Methods

Figure 5.3: Segmentation examples (marked in red) of (a) a healthy segment, (b) a segment with calcium adjacent to one side of the lumen, and (c) a segment with calcium surrounding the lumen.

Path approach [30]. Costs are based on a medialness measure [37] which yields a high response in the lumen center and an intensity based measurement which yields a low response in the background. This step requires three seed points, one for the internal, external and common branch of the carotid arteries.

After obtaining the carotid lumen centerlines, the carotid lumen is segmented using a levelset method. This levelset framework [100] utilizes gradient magnitude information, intensity information along the centerline and information of hyper-intense voxels in the neighborhood to deal with calcifications. The parameters of the segmentation method were optimized using the training data sets of the carotid stenosis quantification challenge [112, 40]. The segmentation examples are shown in Fig. 5.3.

Stenosis Quantification Method

Stenosis quantification is based on the segmented lumen. From the automatically extracted internal and external centerline, the bifurcation point is defined as the position where the distance between the internal and external centerline is 2 mm. The stenosis is quantified within 5 cm distal to the bifurcation point in the internal branch. This range is similar to the range used in the protocol of the challenge [40], where the stenosis is quantified within 4 cm from the bifurcation slice (where the surface starts splitting from the common branch). It is also the clinically most relevant region, as most stenoses occur in this range. The stenosis is quantified using the NASCET criterion, the relative reduction in % of the lumen at the location of the minimal lumen diameter, with respect to the lumen diameter at the reference position. The diameter is measured in MPR images created perpendicular to the automatically extracted centerline and is defined as the shortest axis that equally divides the cross sectional segmentation in two. The reference axis is the average diameter over a length
of 1 cm that starts 2 cm distal to the stenotic segment. More details of this quantification method are presented in the work by Tang et al. [112].

**Statistical Analysis**

To compare the performance of the manual and automatic stenosis categorization, kappa values were calculated from the confusion matrix. We also calculated sensitivity, specificity and positive predictive value (ppv) by defining positives as those cases having a stenosis degree larger or equal than 50% and negatives as those having a stenosis degree < 50%. The threshold of 50% is selected for determining the positives and negatives because stenoses with a degree > 50% benefit from endarterectomy if treated quickly after the ischemic event [91]. The automatically obtained minimal diameter is compared to the manual one using Pearson correlation and Bland Altman analysis.

### 5.3 Experiments and Results

Three types of analyses are performed: 1) stenosis categorization on Set CTA-A, 2) stenosis quantification on Set CTA-A and Set DSA, and 3) quantification of minimal and reference diameter on Set CTA-B.

The lumen segmentation method was applied to 404 carotid arteries of which 363 were suitable for stenosis categorization. The 41 unsuccessful cases can be grouped in three categories: failures of centerline extraction, failures of level set segmentation, and cases that did not comply with the stenosis quantification protocol. The centerline extraction method failed in 22 cases owing to: 1) the estimated centerline going into a nearby vein due to severe lumen narrowing or lack of contrast between the foreground and background (10 cases), 2) the centerline going into bone in regions with severe lumen narrowing which are in close proximity to bone (3 cases), 3) centerline traced from internal to external branch or vice versa (9 cases). The levelset segmentation failed in eight cases because of: 1) lack of contrast between the fore- and background caused by artifacts due to metallic dental implants (5 cases), 2) extremely curved carotid geometries (3 cases). Finally, eleven carotid arteries did not comply with the quantification protocol because the segmented internal branch was too short, i.e. the internal seed point had to be clicked below reconstruction artifacts caused by metallic dental implants.

The 128 carotid arteries whose estimated stenosis degree was non-negative were used for stenosis quantification and quantification of minimal and reference diameter. Among the 128 carotid arteries, the centerline extraction method failed in 8 carotid arteries, and there was one additional failure in the segmentation
5.3. Experiments and Results

Table 5.1: Confusion matrix (displaying (dis)-agreement in assigning stenoses to four risk categories) by the automatic method and the manual method for the 363 carotid arteries in Set CTA-A.

<table>
<thead>
<tr>
<th></th>
<th>0%-29%</th>
<th>30%-49%</th>
<th>50%-69%</th>
<th>70%-100%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automatic</td>
<td>295</td>
<td>19</td>
<td>0</td>
<td>1</td>
<td>315</td>
</tr>
<tr>
<td>Manual</td>
<td>12</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>0%-29%</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>30%-49%</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>317</td>
<td>36</td>
<td>4</td>
<td>6</td>
<td>363</td>
</tr>
</tbody>
</table>

step. Two carotid arteries had an internal branch shorter than 4 cm and did not comply with the stenosis quantification protocol. Eventually, 117 carotid arteries were included in the analysis.

In Set DSA, three cases were not included in the analysis since they have an incorrect automatic centerline. Eventually, 25 carotid arteries were taken into analysis.

5.3.1 Stenosis Detection

Stenosis detection performance was evaluated on the 363 carotid arteries of Set CTA-A, with manual stenosis category labeling as reference standard. Table 1 shows the confusion matrix between the automatically assigned stenosis category and the manually labeled stenosis category. In 308 out of 363 cases the automatically obtained stenosis category and the manually obtained stenosis category are in agreement. Since patients with a stenosis of 50-69% will receive the same treatment as 70-100% patients [100], we define the true positives to be stenosis > 50% and true negatives to be stenosis < 50%. The confusion matrices with four and two risk categories are shown in respectively Tab. 5.1 and Tab. 5.2. We obtained a sensitivity of 0.90 (9/10), a specificity of 0.95 (334/353), and a positive predictive value of 0.32 (9/28). The ability of our method to discriminate significant stenoses from non-significant ones is very limited as in the tested positives, only 32% of them are true positives.

5.3.2 Absolute Stenosis Error

The absolute stenosis error was calculated for all 363 carotid arteries in Set CTA-A. The mean absolute stenosis error is 11.25%. However, the stenosis error in each stenosis category was differently distributed. For stenoses in the range 0-29%, 30-49%, 50-69% and 70-100%, the mean absolute stenosis error
Table 5.2: Confusion matrix (two risk categories) showing (dis)agreement between the automatic method and the manual method for the 363 carotid arteries in Set CTA-A.

<table>
<thead>
<tr>
<th></th>
<th>Automatic</th>
<th>Manual</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%-49%</td>
<td>334</td>
<td>0-49%</td>
</tr>
<tr>
<td>50%-100%</td>
<td>1</td>
<td>50%-100%</td>
</tr>
<tr>
<td>Total</td>
<td>353</td>
<td>20</td>
</tr>
</tbody>
</table>

was respectively 9.34%, 15.96%, 25.58%, and 36.84%. In this large dataset we did not have measures for the inter- and intra-observer variability. As a reference value, in the challenge [40], a mean absolute diameter based inter-observer variability of 7.4% was reported. The mean absolute stenosis error between the automatic method and the ground truth is larger than this inter-observer variability.

We also compared the automatic stenosis degree to the manual stenosis degree in Set DSA. The mean absolute stenosis error is 22.20%, while the mean absolute stenosis error between the manual stenosis degree in CTA and in DSA is 14.69%.

### 5.3.3 Minimal and Reference Diameter Quantification

The minimal and reference diameter were quantified for 117 carotid arteries. Pearson regression analysis shows that the correlation coefficient between the manual and automatic minimal diameter is 0.66. Fig. 5.3(a) shows the scatter plot and Fig. 5.3(b) the Bland Altman [11] plot of the manually and automatically derived minimal diameter. Both plots show that the automated method slightly overestimated the minimal diameter for small diameters and underestimated it for large diameters. The mean difference is -0.33 mm and the limits of agreement are -1.89 mm and 1.24 mm.

Pearson regression analysis shows that the correlation coefficient between the manual and automatic reference diameter is 0.69. Fig. 5.4(a) shows the scatter plot and Fig. 5.4(b) the Bland Altman plot of the manual and automatic reference diameter. The plots show that the reference diameter is slightly underestimated by the automatic method. The mean is -0.74 mm and the limits of agreement are -0.19 mm and 1.68 mm.
5.4 Discussion and Conclusion

In this chapter, automated stenosis quantification in CTA has been evaluated on data that have been acquired in a large prospective study. The segmentation required only three user-clicked seed points to initialize the automatic extraction of the lumen centerlines. The stenosis quantification processing pipeline was successful in 363 out of 404 carotid arteries (90% of the cases). Failures were caused by lack of contrast between the fore- and background owing to (i) adjacent vessels and (ii) teeth metal artifacts. Improvements in image resolution may address the former issue, and excluding the teeth metal from the field of view could address the latter. Alternatively, additional user interaction, for example clicking more seed points in vessel segment that suffer from poor contrast, may increase success rate.

The evaluation shows that the method is able to quantify the minimal diameter and reference diameter with a correlation coefficient of 0.67 and 0.69.

Figure 5.4: (a) Scatter plot and (b) Bland Altman plot of the manual and automatic minimal diameter

Figure 5.5: (a) Scatter plot and (b) Bland Altman plot of the manual and automatic reference diameter
Furthermore, the method achieves a smaller mean stenosis error (11.3%) than was achieved in a public challenge (19.2%). The mean absolute stenosis error increased with the stenosis degree. However, the mean absolute stenosis error between our method and the ground truth is still much larger than the inter-observer variability reported in a public evaluation framework [40]. The method in particular has limited agreement with the observers in detecting stenosis larger than 50% ($\kappa=0.04$, $ppv = 0.32$).

The method obtained a smaller mean absolute stenosis error in this study compared to the results on the challenge data. This is mainly caused by the distribution of stenoses over categories. In this study, most of the patients had a stenosis degree smaller than 29% and our automatic method performs better in this category than in the severe stenosis category. This observation reveals that the patient inclusion protocol can significantly influence the evaluation results of a method. In the 351 patients (702 carotid arteries), 582 carotid arteries have a stenosis smaller than 29% (82.9%), 46 carotid arteries have a stenosis in between 30% and 49% (6.6%), 27 carotid arteries have a stenosis in between 50% and 69% (3.9%) and 47 carotid arteries have a stenosis larger than 70% (6.7%). Despite the higher frequency of carotid arteries with a stenosis degree smaller than 49%, it is especially important to diagnose moderate and severe stenosis ($\geq$50%) accurately, since both patients with a severe stenosis of 70%–100% and a moderate stenosis of 50% - 69% benefit from endarterectomy if treated timely [91].

The mean stenosis error of the automatic method increases with stenosis degree. Both the smaller lumen and the more complex background, including calcifications, are probably the cause of this. Both pose challenges for lumen segmentation. The method tends to over-segment the lumen and hence over-estimates the minimal diameter in cases with severe stenosis. As a result, the method tends to underestimate the stenosis degree for severe stenoses causing a large number of false negatives (19 cases among 28 positives).

For the stenosis categorization, we obtain a kappa value of 0.04, and a ppv value of 0.32, which are both relatively low. This indicates that the method is currently not sufficiently accurate for detecting moderate and severe stenosis. We think that this is currently still a major challenge for stenosis detection in general. For example, even though the anatomy and stenosis definition is different, in the coronary stenosis quantification and detection challenge [18], also a low ppv value (26% for the best detection method) for detecting stenosis over 50% was obtained by the method ranked the best in the stenosis detection category [20].

Strength of our study is that we collected a large prospective sample. A limitation of our study is that all data was acquired on the same Siemens scanner with the same scanning protocol. For the application of this method in scans
obtained with different vendors and different protocols, a retraining of the parameter may be necessary.

To conclude, in a prospectively collected CTA dataset we performed an extensive evaluation of a carotid artery stenosis detection and quantification method which was previously evaluated in a public challenge. The method shows good correlation in quantifying minimal and reference diameter, but it has limited agreement in categorizing severe stenosis. Since severe stenoses are clinically more relevant than mild ones, the method is not yet suitable for use in clinical practice for treatment planning. In the future, efforts should be put in developing or improving methods for detecting, segmenting and quantifying stenosis degree in case of severe stenosis.
Chapter 5. Evaluation of Semi-automatic CTA Carotid Stenosis
Quantification in Patients with TIA or Minor Stroke
In this thesis, we developed, evaluated and applied methods for automatic quantification of imaging biomarkers in CTA and MRI that are relevant for studying, detecting, and diagnosing carotid artery disease. In this chapter we summarize our contributions in each chapter and discuss future research directions.

6.1 General Discussion

Carotid artery geometry may have an influence on the progression of carotid atherosclerosis. Studies investigating the relation between carotid artery geometry and (progression of) atherosclerotic disease have so far been based on manual delineation of centerlines and lumen. This is a tedious procedure, prone to inter- and intra-observer variability, and hence difficult to introduce into clinical practice. Therefore, in Chapter 2 we developed an automated method to quantify the carotid bifurcation angle, carotid ratio and centerline tortuosity based on multisequence MRI data, based on carotid lumen segmentation.

Our method consists of three steps: 1) accurately extracting the internal and external centerline based on three user-clicked seed points using an iterative minimum cost path approach, 2) segmenting the lumen with a geodesic active contour using the centerline as initialization and local intensity information to guide the segmentation, 3) quantifying parameters related to the carotid artery geometry from the extracted centerline and segmented lumen. The methods for centerline tracking and lumen segmentation are evaluated by comparing their accuracy to the inter- and intra-observer variability on 48 datasets (96 carotid arteries). The correlation coefficients between manually and automatically derived bifurcation angle, carotid proximal area ratio, carotid proximal bulb size and vessel tortuosity quantifications are close to the correlation be-
between observers. This demonstrates that the automated method can be used to replace manual centerline annotation and manual contour drawing for lumen segmentation in MRI data for quantifying the carotid bifurcation geometry.

The automatic iterative centerline extraction method presented in Chapter 2 for carotid arteries solves the short-cutting property of standard minimum cost path approaches. Although this method was developed in MRI for carotid arteries, it was also shown to be suitable for carotid arteries in CTA and coronary arteries in CTA [5, 16, 102, 103]. We believe that this method has the potential to become a standard tool for obtaining accurate centerlines.

The degree of stenosis is an important biomarker in assessing the severity of cardiovascular disease. In Chapter 3, we presented an automatic stenosis detection and quantification method based on lumen segmentation in CTA. The lumen of the carotid arteries was segmented in three steps. First, the internal and external centerlines were extracted with the iterative minimum cost path approach, developed in Chapter 2. Second, the lumen boundary was delineated using a level set method which was steered by gradient information, regional intensity information, and spatial information. A novel aspect of the segmentation method is the use of a regional intensity term in addition to the gradient magnitude to steer the level set evolution. This term accounts for strong local variations in background caused by plaques. Third, side branches in the segmented lumen were removed by applying a shape constraint in which the shape was defined as the envelop of the maximum inscribed cylindrical surface of the segmentation. The method was trained and tested on a publicly available database from the cls2009 challenge [40]. For the segmentation, we obtained a Dice coefficient of 90.2%, and a mean absolute surface distance of 0.23 mm, which implies that the method ranked second among 10 methods. For stenosis quantification, an average error of 16% was obtained which made it rank first among the submitted stenosis quantification methods.

In Chapter 4, we presented and evaluated a method for automatic intra-plaque hemorrhage segmentation and subsequent volume quantification in T1w-MRI. This method models the intensity of the IPH and the background in T1 weighted MRI to be smoothly varying. Segmentation was performed with a piecewise-smooth regional level set method, which was initialized by user-clicked seed points. We trained the method on 18 datasets and evaluated the IPH segmentation method on 22 carotid arteries. We also evaluated the robustness w.r.t. manual initialization by manually clicking two sets of seed points and assessing the reproducibility of the volume quantification. We showed that semi-automatic segmentation and quantification of intra-plaque hemorrhages is feasible. The method’s accuracy was similar to the inter-observer variability. The method demonstrated excellent reproducibility w.r.t. rescanning and manual initialization, outperforming manual reproducibility. We hence conclude that
the developed method is a promising tool for replacing manual intra-plaque hemorrhage volume quantification.

In Chapter 5, we evaluated the automatic CTA-based carotid stenosis quantification method from Chapter 3 on a large set of 404 carotid arteries. In the evaluation we used additional metrics compared to the ones used by the cls2009 challenge. The method successfully segmented 363 out of 404 carotid arteries in CTA. It achieved a correlation of 0.66 and 0.69 between the manually and automatically measured minimal and reference diameter. The mean absolute error in stenosis degree between manual and automatic method was 11.25%. The stenosis category from the method agrees in 308 out of 363 carotid arteries with the manual scoring (\(\kappa = 0.04\), ppv = 0.32, sensitivity = 0.95, specificity = 0.9). We also compared the estimated stenosis degree with a DSA-based stenosis measurement. The mean difference in stenosis degree between manual stenosis assessment in DSA and the automatic method was 23.14%. For comparison, the mean difference in stenosis grade between manual stenosis assessment from DSA and CTA was 15.89%. These results indicate the potential of the method, but there is still limited agreement with the manual method in categorizing severe stenosis (only 9 of 28 true positives were detected).

6.2 Future Perspectives

Future work could be both directed to further improving the methodologies, and in evaluating and applying the method in different settings.

With respect to the methodology, steps towards full automation could be taken: Most approaches, including the ones presented in this thesis, are not fully automatic. The lumen segmentation methods need three user-clicked seed points for initialization and the intra-plaque hemorrhage segmentation method needs the users to click in the center of every intra-plaque hemorrhage spots. Automatic seed point detection would fully automate the biomarker quantification procedure. Some work has already been done, e.g. to detect seed points in coronaries [78]. For cerebral arteries, Manniesing et al. [76] automatically detected the seed point on the basis of the classic Shannon entropy measure [104] and the Hough transform [50]. We also think that registering a target image to atlases where the seed points are available is a possible approach to replace manual seed point clicking.

Also, the evaluation of the semi-automatic CTA carotid artery stenosis quantification method in Chapter 5 showed that quantifying severe stenoses is still an issue due to the complicated image context in the plaque area. Before this approach can be applied, either in the context of clinical studies, or in clinical practice, efforts should be made in increasing the accuracy in presence of se-
vere stenoses. Several factors may cause the current low performance in case of severe stenoses. Blurring artifact caused by the system’s point spread function may add uncertainty for the method to delineate the lumen border, which may especially hamper regions where the remaining lumen is small. In this case, a lumen segmentation method that incorporates prior information on image acquisition physics and reconstruction, may be of help. For MRI data, some methods have been proposed to incorporate the image acquisition physics into segmentation algorithms [88, 87]; these methods may inspire future segmentation tasks in CTA.

With respect to the performed evaluation we should stress that the methods developed in Chapter 2 and Chapter 4 were developed for and evaluated on data of the Rotterdam study. These datasets were scanned with a standardized protocol. In these chapters we did not investigate whether the methods can be used on images acquired on different scanners and/or with different acquisition settings. Additional evaluation of the methods should be performed on data scanned with different protocol on scanners from different vendors to assess the applicability of the methods in different settings; in this case, a parameter retraining may be required. Note that in chapter 3, we evaluated our method on a publically available platform [40] which contains multi-center and multi-vendor datasets.

Also, in Chapter 2 and Chapter 3, we did not evaluate the method’s performance on its reproducibility with regard to repeated scans. For the application of the presented methods on longitudinal datasets, the inter-scan reproducibility is important, to properly interpret the estimated change in the biomarker over time.

Evaluating a method on large representative datasets is essential for a thorough assessment of a presented method. However, collecting a large and representative dataset and the ground truth requires an enormous effort. Currently, data used for evaluations reported in the literature is often not publicly available for other researchers to use. There are, however, an increasing number of challenges containing multi-vendor multi-center scans that provides a standardized evaluation framework for medical image analysis methods (http://www.grand-challenge.org/index.php/All_Challenges) [57, 40, 94]. As such frameworks allow for objective performance assessment and comparison of algorithms, they are an important step towards the take-up and acceptance of imaging biomarkers in clinical research and eventually in clinical practice.

With respect to additional application of the method, in this thesis we only applied the method in a cross-sectional setting. By applying the semi-automatic segmentation and quantification methods to longitudinal clinical data, the change in the biomarkers over time can be obtained and associated with carotid artery disease progression. We expect that change in such biomarkers will also
be important in carotid artery disease diagnosis and therapy planning.

6.3 Conclusion

In conclusion, this thesis demonstrated that: 1) The carotid artery centerline can be semi-automatically extracted with an accuracy comparable to the experts based on three manually selected seed points. The carotid artery lumen can be automatically segmented with an accuracy close to the experts based on the extracted centerlines in BBMRA. The carotid geometry can subsequently be quantified from the automatically segmented lumen. 2) The lumen of an atherosclerotic carotid artery can be semi-automatically segmented with high accuracy in CTA, but stenosis quantification of the carotid lumen is still a challenge, especially for severe stenoses. 3) Using a semi-automated method, the intra-plaque hemorrhage volume can be quantified with a higher robustness with respect to seed point selection and with a higher inter-scan reproducibility compared to manual assessment by experts.
Chapter 6. Conclusion and Future work

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Curriculum Vitae

Hui Tang was born in Jiangsu, China. She obtained her B.E degree (in 2006) and M.E. degree (in 2009) both in Electronic Science and Engineering from Southeast University, Nanjing, China. Since July 2009, she became a PhD student in the Quantitative Imaging group, Delft University of Technology, the Netherlands and Biomedical Imaging Group Rotterdam (BIGR), Erasmus MC, the Netherlands. She was involved in the vascular image analysis theme group, focusing on the carotid artery lumen segmentation and biomarkers quantification.
Publications

Journal Papers:


Conference Papers:

wall segmentation by coupled surface graph cuts, MICCAI Medical Computer Vision Workshop, 2012


Miscellaneous:

Conference Abstracts:


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