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Lumen segmentation and stenosis quantification of atherosclerotic carotid arteries in CTA utilizing a centerline intensity prior

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Purpose: 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 semiautomatic method for carotid lumen segmentation and subsequent carotid artery stenosis quantification in CTA images.

Methods: The authors present a semiautomatic 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, the authors detect and quantify the cross-sectional area-based and cross-sectional diameter-based stenosis degrees according to the North American Symptomatic Carotid Endarterectomy Trial criterion.

Results: The method is trained and tested on a publicly available database from the cls2009 challenge. For the segmentation, the authors obtain a Dice similarity coefficient of 90.2% and a mean absolute surface distance of 0.34 mm. For the stenosis quantification, the authors obtain an average error of 15.7% for cross-sectional diameter-based stenosis and 19.2% for cross-sectional area-based stenosis quantification.

Conclusions: With these results, the method ranks second in terms of carotid lumen segmentation accuracy, and first in terms of carotid artery stenosis quantification. © 2013 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4802751]

Key words: geodesic active contour, gradient magnitude, regional intensity, calcium, envelope of the maximum inscribed spheres

I. INTRODUCTION

The latest report from WHO shows that cardiovascular diseases are the leading causes of death and disability in the world.1 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. For diagnosis and treatment planning, accurate stenosis quantification on CTA would be required. We aim to develop a semiautomatic 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), one established by the European Carotid Surgery Trial (ECST), and the common carotid (CC) method. In (semi)automatic quantification, the NASCET is commonly used, 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. first performed an internal carotid branch segmentation and then quantified the stenosis degree at manually annotated positions. Similarly, Zuluaga et al. performed segmentation before stenosis detection and grading. They located the stenosis at the centerline location where the CSA is minimal. Kelm et al.9 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. 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, graph cuts, and level sets, including level sets using boundary information, using global regional information and using variational local regional information. Vessels are usually modeled as tubular structures. The tubular pattern is maintained by minimizing the minimal principal curvature in level sets or by restricting the distance to centerlines in graph cuts.

Graph cuts and level sets 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. extended the Chan-Vese 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 nonuniformity of the contrast agent. This method was evaluated on ten internal carotid branches. Krissian and García also used the level sets extraction scheme steered by gradient magnitude information. Gülşün and Tek segmented the carotid arteries using a graph cut approach. The novelty in their work is that they normalized the edge weight by the distance to centerlines to remove nonisolated topology caused by side branches or nearby veins. Manniesing et al. utilized both gradient magnitude and intensity information to steer a level set evolution. Tang et al. 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 semiautomatically extracted centerline. Ukwatta et al. 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, in the segmentation step, or as a post-processing step. Schaap suppressed calcium using intensity based kernel regression. In this method, hyperintense areas are labelled as outliers and those areas are assigned an intensity which are much lower than the normal lumen intensity. Manniesing and Niessen applied a mask to remove calcium and bone. Scherl et al. segmented calcium and lumen simultaneously using a modified Chan-Vese model in which calcium is removed by a intensity-based regularization term. Gülşün and Tek excluded calcium by setting the ascending gradient from the centerline to zero. Cuisenaire removed the calcium by applying a threshold to the segmented foreground. In all these methods, only Scherl et al. 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 removed outliers in a postprocessing 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. 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, 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 paper, we present a semiautomatic 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 to achieve an accuracy comparable to interobserver variability, especially in curved regions, with cost defined in an image after hyperintense suppression (suppressed using the initial centerlines). Second, we extend the geodesic active contour 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 paper is organized as follows: Section II describes the method. Section III describes the data, the parameter optimization, and the results. We discuss the results and conclude in Sec. IV.

II. 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. Subsections II.A–II.D describe each step for the segmentation and stenosis grading.

II.A. Centerline extraction

Centers 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 multiplanar reformatted image stack generated perpendicular to the centerline from the previous iteration. More details of this approach are provided in Refs. 25 and 38. To address the second drawback, we suppress hyperintense regions as follows:

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

where $I_p(x)$ is the intensity after hyperintense 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. (1) is shown in Fig. 1. Intensity fluctuations that are only slightly higher than the estimated lumen intensity will only be marginally affected by the hyperintensity suppression. In Fig. 2, we show an example of the medialness measure applied to both the original image and the hyperintense-suppressed image. The green contour denotes the manual segmentation and the green marker points to the position with maximal medialness. The maximal mediality in which calcium has been suppressed is located more towards the lumen center for images with hyper-intense suppression.

II.B. Lumen segmentation

A geodesic active contour35, 39 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.
FIG. 2. Medialness computation with and without hyper-intense suppression. (a) Original image, (b) medialness of original image, (c) hyperintense suppressed image, and (d) medialness of hyperintense suppressed image.

since calcified regions adjacent to the lumen yield an even higher value of the gradient magnitude. Figure 3(c) shows an example of the gradient magnitude of a carotid artery in CTA. In this case, the gradient between lumen 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 Figs. 3(b)–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:

\[ E(S) = \gamma \int \int_S P(I(S(u, v)))|S(u, v)| du dv + \alpha \int \int_{\Omega_1} (1 - s(x))dxdydz + \beta \int \int_{\Omega_2} s(x)dxdydz. \]  

(2)

\( u \) and \( v \) are used for parameterizing the surface \( S \), i.e., for points on the surface,\(^{39}\) 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. (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 \( \sigma \), \( \frac{1}{|G_{\sigma g}I| + \eta} \). \( \eta \) is a small positive value to prevent dividing by zero. \( s(x) \) determines the similarity of a voxel to the lumen:

\[ s(x) = e^{-\frac{(I(x) - \bar{I}_c)^2}{\sigma^2}}. \]  

(3)

Here \( \bar{I}_m(x) \) 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 \( \bar{I}_m(x) \) is defined by

\[ \bar{I}_m(x) = \bar{I}(\arg\min_{x_c}(d(x, x_c))), \]

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

(4)

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 \( \sigma \) 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

FIG. 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, and (d) gradient magnitude of original CTA overlaid by manual segmentation and segmentation using only boundary information.
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. (2) will contain the voxels surrounding calcium. Figure 4(a) shows the original image with the manual segmentation overlaid in red and the voxels surrounding calcium. Figure 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 Figs. 4(c) and 4(d).

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

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

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

\[
CN(x) = C(x) \oplus \mathcal{N}_x,
\]

where \(T_c\) is experimentally selected. \(\mathcal{N}_x\) is a cube of size 5×5×5 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.

\[
E(S) = \gamma \iiint P(I(S(u, v)))|S(u, v)|dudv + \alpha \iiint_{\Omega_1} (1 - s(x))dxdydz + \beta \iiint_{\Omega_2} s(x)dxdydz + \delta \iiint_{\Omega_1} CN(x)dxdydz.
\]

Replacing \(S(u, v)\) by a level set function \(\phi(x)\), which is negative inside surface \(S(u, v)\) and positive outside \(S(u, v)\) (Ref. 40) in Eq. (7), and replacing region \(\Omega_2\) by the Heaviside function \(H_c(\phi(x))\), region \(\Omega_1\) by \(1 - H_c(\phi(x))\), we get

\[
E(\phi) = \gamma \iiint (H_\epsilon'(\phi(x))P(I(\phi(x)))(\nabla \phi(x)) + \alpha(1 - H_c(\phi(x)))(1 - s(x))|\nabla \phi(x)| \]

\[
+ \alpha(1 - s(x))|\nabla \phi| + \beta H_c(\phi(x))s(x)|\nabla \phi| + \delta (1 - H_c(\phi(x))CN(x))|\nabla \phi|dxdydz. \tag{8}
\]

Minimizing Eq. (8) by gradient descent yields

\[
\phi_t = H'_\epsilon(\phi(x))\frac{\partial}{\partial \gamma} P(I(\phi(x)))|\nabla \phi| + \alpha(1 - s(x))|\nabla \phi| + \beta s(x)|\nabla \phi| - \delta CN(x)|\nabla \phi|.
\]

For tubular structure segmentation, \(\kappa\) is changed to be the minimum principal curvature. \(\kappa\) There are five terms in Eq. (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 $\gamma_a$.

II.C. Side branch removal

Side branches may occur in the distal region of the external and internal branches. The segmentation obtained from Eq. (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. Figure 5(a) shows an example with side branches. Along the centerline, we extract the curved multiplanar reformatting (CMRP) image. The surface in Fig. 5(a) is colored in those regions where the surface distance between the manual segmentation and the semiautomatic segmentation is over 0.5 mm. The image at the level of the side branch is shown in Fig. 5(c), and the corresponding segmentations are shown in red in Fig. 5(d) (manual: green, semiautomatic: red, overlap: 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.vmtk.org). 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. 5(b). However, 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 Figs. 6(a) and 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 Figs. 7(a) and 7(b). The green curve is the long axis before smoothing and the red curve is the long axis after smoothing. From Fig. 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. 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 semiautomatic segmentation will be considered as an indication of side branch
FIG. 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 and (b) carotid artery without side branch but a stenosis.

if it is over 1 mm, shown in the dash blue line in Figs. 7(a) and 7(b).

II.D. Stenosis detection and grading

We quantify the stenosis using the NASCET criterion.

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., CSA and 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. 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 in depicted in Fig. 9.

FIG. 8. An example of short axis (diameter).

FIG. 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 and (b) corresponding CSA curve.
III. EXPERIMENTS

III.A. 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.” We implemented the proposed segmentation method in ITK (www.itk.org), ignoring $H'(\phi(x))$ because of the narrow-band implementation ($|\phi(x)| < 3$). 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.vmtk.org). The centerline extraction takes on average 10 min; the level set evolution takes on average 15 min; the side branch removal takes around 20 min; the stenosis quantification takes on average 5 s. All timings were done using a linux 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.

III.B. Parameter optimization

The parameters that were fixed in this method are listed in Table I. 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, 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 six steps, and we include a curvature weight of 0. The advection weight $\gamma_a$ is varied from five to 25 with a step size of five, 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 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. Figure 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. Figures 10(c) and 10(d) show that the curvature weight $\gamma_c$ hardly influences the DSC between 0

![Image](image-url)

**Fig. 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, and (f) as a function of $\gamma_c$ and $T_c$ at $\gamma_a = 20$ and $\alpha = 0$. 

<table>
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<td>Number of iterations</td>
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<td>Initial tube radius (mm)</td>
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<td>$k$ in Eq. (4) (HU)</td>
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<td>$N_x$ size</td>
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and 1. As a result we fixed the curvature weight to 1 and minimize the $SE_a$ and $SE_b$ 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 five, $\alpha$ 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. Figures 11 and 12 show the result of the stenosis quantification error as a function of two out of three parameters when the third one is kept at its optimal value. Table II lists the optimal parameters for three different optimization metrics and the performance according to all three metrics.

### III.C. 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 III 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 MSD is 0.34 mm. The average DSC obtained with the parameters trained by minimizing $SE_d$ is 88.9%, and the MSD is 0.43 mm. We performed a

<table>
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<tr>
<th>Team</th>
<th>Total success</th>
<th>Dice (%)</th>
<th>MSD (mm)</th>
<th>Max (mm)</th>
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<td>Observer A</td>
<td>41</td>
<td>95.1</td>
<td>0.10</td>
<td>0.65</td>
</tr>
<tr>
<td>Observer B</td>
<td>41</td>
<td>94.6</td>
<td>0.11</td>
<td>0.83</td>
</tr>
<tr>
<td>Observer C</td>
<td>41</td>
<td>94.4</td>
<td>0.12</td>
<td>0.91</td>
</tr>
<tr>
<td>Gülşün (Ref. 21)</td>
<td>41</td>
<td>91.8</td>
<td>0.18</td>
<td>1.52</td>
</tr>
<tr>
<td>OursAtMin$SE_a$</td>
<td>41</td>
<td>90.2</td>
<td>0.34</td>
<td>3.45</td>
</tr>
<tr>
<td>OursAtMaxDSC</td>
<td>41</td>
<td>89.3</td>
<td>0.38</td>
<td>3.51</td>
</tr>
<tr>
<td>Krissian (Ref. 26)</td>
<td>41</td>
<td>87.3</td>
<td>0.54</td>
<td>4.42</td>
</tr>
<tr>
<td>Hui Tang (Ref. 29)</td>
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<td>88.9</td>
<td>0.38</td>
<td>3.88</td>
</tr>
<tr>
<td>OursAtMin$SE_d$</td>
<td>41</td>
<td>88.9</td>
<td>0.43</td>
<td>4.09</td>
</tr>
</tbody>
</table>

Figure 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 $\gamma_a = 5$ and (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 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 $\alpha = 0.03$, and (c) as a function of $\alpha$ and $\gamma_a$ at $T_c = 180$ HU.
TABLE IV. Paired *t*-test of segmentation performance between Tang *et al.* (Ref. 29) (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>
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<tr>
<th>p value</th>
<th>SegHT</th>
<th>SegMaxDSC</th>
<th>SegMin$SE_a$</th>
<th>SegMin$SE_d$</th>
</tr>
</thead>
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<tr>
<td>SegHT</td>
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<td>0.449</td>
<td>0.006</td>
<td>0.925</td>
</tr>
<tr>
<td>SegMaxDSC</td>
<td>...</td>
<td>...</td>
<td>0.014</td>
<td>0.329</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>

paired *t*-test to check for statistical significance of the aforementioned difference, also with our previous work. 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 IV. 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 methods that ranked first (Gülsün and Tek21), second (Krissian and García26) and third (Tang *et al.*29). SegMin$SE_a$ ranks second in the segmentation challenge.

After applying the side branch removal step, the side branches are successfully removed, shown in Figs. 13(a) and 13(b). Example results of the proposed segmentation method obtained at parameters trained to maximize DSC are shown in Figs. 14(a) to 14(f). In all cases, the plaque tissue is not included in the segmented lumen. With the CN term in the

![FIG. 13. Example of the side branch removal.](image1)

![FIG. 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), semiautomatic method (red), overlap (yellow). (a)–(c) Semiautomatic segmentation without the term for excluding voxels around calcium. (d)–(f) Semiautomatic segmentation with the term for excluding voxels around calcium.](image2)

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The energy function of Eq. (8), the voxels around calcium are also excluded from the segmentation.

### III.D. 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 V. 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 method that ranked first (MARACAS). MinAreaStenosis ranks first in the stenosis quantification challenge.

### III.E. Reproducibility with respect to user interaction

We also investigated the reproducibility of the method in view of the minimal user action (selecting three seed points) required. We automatically apply a random 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 carotid arteries. 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.

We performed centerline extraction, segmentation and stenosis quantification with the repositioned seeds on 15 training data sets. Reproducibility with respect to 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 VI.

### IV. DISCUSSION AND CONCLUSION

We developed and quantitatively validated a semiautomatic 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, 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 Gülşün and Tek who ranked first. Compared to our own previous work which does not address voxels around calcium.

### Table V. Averages stenosis.

<table>
<thead>
<tr>
<th>Team name</th>
<th>Total success</th>
<th>$SE_a$ (%)</th>
<th>$SE_d$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>41</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Observer A</td>
<td>41</td>
<td>3.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Observer B</td>
<td>41</td>
<td>5.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Observer C</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 (Ref. 8)</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>

### Table VI. 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>$SE_a$ (%)</th>
<th>$SE_d$ (%)</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>
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 mis-segmentation 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 with respect to carotid artery stenosis quantification, slightly higher than the MARCAS 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 second in the carotid artery challenge, and with respect to segmentation than for carotid artery stenosis quantification. With different parameter settings are optimal for 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.

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