Semiautomatic carotid lumen segmentation for quantification of lumen geometry in multispectral MRI

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ABSTRACT

Quantitative information about the geometry of the carotid artery bifurcation is relevant for investigating the onset and progression of atherosclerotic disease. This paper 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 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 tortuosity 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.

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1. Introduction

Carotid atherosclerosis, i.e. plaque build-up in the arterial wall, is a major cause of mortality and morbidity (Ross, 1999). A large number of research institutes have studied the factors affecting plaque formation and growth (Chambless et al., 1997; Berenson et al., 1998; Stensland-Bugge et al., 2001; Lee et al., 2008). Friedman et al. (1983) 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 (Thomas et al., 2005; Smedby and Bergstrand, 1996). Thomas et al. (2005) showed that variation in carotid bifurcation geometry significantly increases with age and early atherosclerotic disease progression. In a longitudinal study, Smedby and Bergstrand (1996) showed that plaque progression was associated with a high mean value of vessel tortuosity in femoral arteries. Lee et al. (2008) 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.

Carotid MRI is a histologically validated method for visualizing atherosclerosis progression and regression (Underhill et al., 2010). The current work is being carried out in the context of a population study (Hofman et al., 2009), 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 (Yuan et al., 1999; Ladak et al., 2001; Jin and Ladak, 2004; Adame et al., 2004; Manniesing et al., 2010; Bijari et al., 2011; Krissian and García, 2009), using explicit contours or surface deformation schemes such as snakes (Kass et al., 1988) and geodesic active contours (Caselles et al., 1997a). There exist several ways to categorize lumen segmentation methods (Lesage et al., 2009), in this paper we discuss the deformable model based carotid lumen segmentation methods according to the type of image features used: gradient only (Yuan et al., 1999; Ladak et al., 2001; Jin and Ladak, 2004; Adame et al., 2004; Bijari et al., 2011) or a combination of intensity and gradient features (Tang et al., 2010; Manniesing et al., 2010; Krissian and García, 2009).

In the first category, Yuan et al. (1999) 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. (2001) 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 and Ladak (2004) 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 et al. (2011) segmented carotid arteries in 122 Contrast-Enhanced MRA datasets using level set evolution.

In the second category, Tang et al. (2010) 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. (2010) 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 (Hameeteman et al., 2009), Krissian and García (2009) evolve the levelset using both intensity and gradient information in 41 carotid arteries.

In this paper 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 (Hofman et al., 2009). 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. 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 paper 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 paper in Section 4.

2. Methods

The data used in our work is from the Rotterdam Study (Hofman et al., 2009) 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. 1, and details on all four stages are presented below.

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. (1998) 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 suffers less from intensity inhomogeneity than BBMRI. Optionally, an anisotropic edge enhancement diffusion filter (Weickert, 1998) 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 varia-
tion, we apply an intensity normalization such that the images have zero mean and unit variance. All parameters in the pre-processing part are fixed and are described in the parameter selection section. Fig. 1 shows the BBMRI and PCMRA before and after preprocessing.

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 (Gülsün and Tek, 2008) and the similarity of the local image intensities to the image intensities at the position of the seed points (Tang et al., 2011). 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 (CMRP) 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:

\[
E(C) = \int P(C(p)) |C'(p)| dp,
\]

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.

2.2.1. Cost function and minimum cost path

Our cost function includes two terms: medialness \( m(x) \) (Gülsün and Tek, 2008) 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 Gülsün and Tek (2008). The lumen similarity measure is based on the voxel intensity. Parameters that tune the contrast of the cost image are commonly incorporated in the 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:

\[
P(x) = \frac{1}{\epsilon + m(x)^a s(x)^b},
\]

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 track-
ing robustness. The multispectral medialness is defined to be the maximum medialness of the two images:
\[
m(x) = \max(m_{\text{BB}}(x), m_{\text{PC}}(x)),
\]
where \(m_{\text{BB}}\) and \(m_{\text{PC}}\) 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:
\[
s(x) = \max(s_{\text{BB}}(x), s_{\text{PC}}(x)),
\]
where \(s_{\text{BB}}\) and \(s_{\text{PC}}\) 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:
\[
s_{\text{BB}}(x) = \begin{cases} e^{-\frac{1}{2} \left( \frac{m_{\text{BB}}(x) - \mu_{\text{BB}}}{\sigma_{\text{BB}}} \right)^2}, & I_{\text{BB}}(x) > \mu_{\text{BB}} \\ 1, & I_{\text{BB}}(x) \leq \mu_{\text{BB}} \end{cases}
\]
and
\[
s_{\text{PC}}(x) = \begin{cases} e^{-\frac{1}{2} \left( \frac{m_{\text{PC}}(x) - \mu_{\text{PC}}}{\sigma_{\text{PC}}} \right)^2}, & I_{\text{PC}}(x) < \mu_{\text{PC}} \\ 1, & I_{\text{PC}}(x) \geq \mu_{\text{PC}} \end{cases}
\]

The standard deviations (\(\sigma_{\text{BB}}\) and \(\sigma_{\text{PC}}\)) and the mean intensities (\(\mu_{\text{BB}}\) and \(\mu_{\text{PC}}\)) 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. Fig. 2a shows the medialness response of preprocessed BBMRI in Fig. 1 while Fig. 2b depicts the lumen intensity similarity response. Fig. 2c and Fig. 2d show corresponding response profile, which shows that medialness provides better lumen center representation while lumen intensity similarity strongly suppresses the background signal.

2.2.2. 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. (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 van Heekeren et al. (2007) 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 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:
\[
P(x) = \frac{1}{e^{m_{\text{BB}}(x)} + \gamma},
\]
where \(\gamma\) controls the cost image contrast. This step is iterated until the centerline converges. Fig. 3a and Fig. 3b provide an example of the original image and the image stack generated by CMPR.

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 cannot 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 (Caselles et al., 1997a; Han et al., 2003) 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 (Caselles et al., 1997b):
\[
E(S) = \int \int P(I(S(u, v)))|S(u, v)|dudv.
\]
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 (Caselles et al., 1997a; Caselles et al., 1997b). However, owing to the limited resolution and

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**Fig. 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
boundary intensity \( I_b \) than 0.5, with lumen intensity in the training data. The ground intensity is estimated as the average over all voxels within a circle with radius \( r \) centered around the centerline. The background intensity is estimated as the average of all voxels within a circle with radius \( r \) that have a local lumen similarity \( S_{\text{local}} \) less than 0.5, with \( S_{\text{local}} \) defined as:

\[
S_{\text{local}}(x) = \begin{cases} 
\exp\left(\frac{-|x|^2}{2\sigma^2}\right), & I(x) > I_{\text{face}}(z) \\
1, & I(x) < I_{\text{face}}(z).
\end{cases}
\]

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. (8) using gradient descent yields the following level set evolution (Caselles et al., 1997a):

\[
\phi_t = P(I(x))k|\nabla \phi| + \nabla P(I(x)) \cdot \nabla \phi,
\]

where \( k = \text{dist}(\nabla^2 I) \) is the mean curvature. In our application, the minimum curvature \( \kappa_{\text{min}} \) is used as we are dealing with tubular structures (Lorigo et al., 2001). The curvature term (first term of Eq. (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. (2003) which evolves only the surface at simple points. A point is a simple point if its addition or removal from the segmentation does not change its topology (Kong and Rosenfeld, 1989). Usually a propagation term that speeds up the evolution is added (Caselles et al., 1997a), thus the level set evolution becomes:

\[
\phi_t = \begin{cases} 
cP(I(x))\kappa_{\text{min}}|\nabla \phi| + P(I(x))|\nabla \phi| + \nabla P(I(x)) \cdot \nabla \phi, & \text{if } x \text{ is a simple point} \\
0, & \text{otherwise}.
\end{cases}
\]

The two parameters \( k \) and \( c \) will be optimized in the experiments.

2.4. Quantification of geometry

Lee et al. (2008) 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 (Antiga and Steinman, 2004). 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 CCA0 and CCA01, which pass through ICA0 and ECA0 respectively, can be found. Shown in Fig. 5a, CCA1 (ECA1, ICA1) is the center of a downstream (upstream) MIS which passes through CCA0 (ECA0, ICA0). CCan (ECan, ICAn) can be determined in a similar way. The four points, i.e. ICA0, ECA0, CCA00, CCA01, are used to define a reference plane (shown in Fig. 5b)
whose normal vector and origin are interpolated using generalized barycentric coordinates, see Antiga and Steinman (2004).

**Bifurcation angle definition:** ECA is a vector from ECA0 to ECA1, ICA is a vector from ICA0 to ICA1. The bifurcation angle is the angle between the projection of the ECA and ICA vector on the bifurcation plane. More details of the bifurcation angle quantification can be found in the work of Antiga et al. (2003) and Thomas et al. (2005).

**Proximal bulb size and proximal area ratio definition:** As defined by Lee et al. (2008), the proximal area ratio is calculated as the ratio between sum of cross-sectional areas (CSA) in ICA1 and ECA1 and cross-sectional area in CCA3, while the bulb size is calculated as the ratio of CSA between ICA1 and CCA3. Due to our imaging protocol, the common artery sometimes is not long enough to find CCA3, as a result we quantified CSA at CCA2 instead of CCA3. For the cases where CCA3 can be calculated, a paired t-test showed that CCA in CCA2 is not significantly different from CCA3 (p > 0.05).

**Tortuosity definition:** Three centerlines, i.e. a local centerline between CCA2 and ICA5, the centerline of the internal branch, and the centerline of the external branch are used for tortuosity quantification. Bullitt et al. (2003) proposed three metrics for 3D tortuosity quantification, i.e. distance metric (DM), inflection count metric (ICM) as well as sum of angle metric (SOAM) for intracerebral vasculature. DM is defined as the ratio between curve length and chord length. Lee et al. (2008) defined the tortuosity as DM subtracted by 1. We follow the definition used by Lee et al. (2008). Beside that since SOAM measures coil-shaped tortuosity, although the relevance of SOAM on atherosclerosis progression has not been investigated yet, we quantified SOAM for each centerline as well. SOAM is defined as an average of root of squared sum of in-plane angle and torsional angle over the whole centerline (Bullitt et al., 2003).

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.

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 $13 \times 13 \text{cm}^2$, a matrix of $160 \times 128$, an in-plane pixel size of $0.51 \times 0.51 \text{mm}$ 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 $18 \times 18 \text{cm}^2$, a matrix of $256 \times 128$, an in-plane pixel size of $0.7 \times 0.7 \text{mm}$ 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.

3.2. Software and implementation

Affine registration from PCMRA to BBMRI was performed using Elastix (Klein et al., 2010). The minimum cost path approach was performed simultaneously from the two seed points using Dijkstra’s algorithm (Dijkstra, 1959). The topology preserving geodesic active contour was based on an ITK implementation (Ibanez et al., 2005). The centerline evaluation software from Schaap et al. (2009), and the segmentation evaluation software from Hameeteman et al. (2009) and Hameeteman et al. (2011) were used. The reference standard was annotated using in-house developed software (Hameeteman et al., 2009) built with MeVisLab (http://www.mevislab.de).

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 artifacts). 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. 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.

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

![Fig. 5. An example of bifurcation decomposition by VMTK: (a) bifurcation vector (black) and decomposed surface (green: external artery, yellow: internal artery, red: common artery) overlayed by maximum inscribed spheres and cross-sections at ECA1, ICA1 and CCA2, (b) bifurcation plane (red), (c) decomposed centerline tree (green: external centerline, yellow: internal centerline, red: common centerline). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](http://www.mevislab.de)
segmentation to the manual ones, the average correlation was determined. We evaluated the segmentation method using two evaluation metrics: the Dice similarity coefficient (DSC) \(\text{DSC (Dice, 1945)}\) and the mean absolute surface distance (MASD) \(\text{Hameetman et al., 2011)}\).

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

#### 3.4.1. 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 \(1e^{-1}\) to \(1e^{-5}\) 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.

#### 3.4.2. Parameter optimization results

Table 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. 7a and 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 decrease 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 iteration, thus \(\gamma\) is set to 1 in each iteration.

Fig. 8 shows the centerline accuracy as a function of the number of iterations. 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 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.

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. 9a and b show the optimization of \(c\) and \(k\) w.r.t DSC after excluding the failed segmentation. Fig. 9c 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 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 initialization were used for initialization.

In conclusion, based on the parameter optimization stage, we choose to use both BBMRI and PCMRA, \(\alpha = \beta = 4, \gamma = 1, k = 0.6,\)

![Fig. 6. Data composition in this work.](image-url)
c = 0.01; we included denoising in the preprocessing, and used centerlines from the third iteration for the algorithm evaluation.

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 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. 10b–e.

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 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. 10b–e.

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.

3.7.1. Bifurcation angle

Carotid bifurcation angles were quantified using both the manual segmentation and the automatic segmentation methods. Fig. 11a shows the scatter plot and the Bland–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 5.

Table 4 indicates that for 30 carotid arteries which have inter- and intra-observer annotations, this correlation is close to the in-
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.

Fig. 11c and 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 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 6.

Fig. 11e and 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 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 4, the Pearson correlation of proximal area ratio between automatic segmentation and manual segmentation is close to those between manual annotations between different observers.

3.7.3. Tortuosity

In the automatic quantification, the centerline extracted by the minimum cost path approach is closer to the manual centerline...
Table 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>
</tr>
</thead>
<tbody>
<tr>
<td>MCD (mm)</td>
<td>DSC</td>
</tr>
<tr>
<td>Intra</td>
<td>0.27</td>
</tr>
<tr>
<td>Inter</td>
<td>0.32</td>
</tr>
<tr>
<td>Auto</td>
<td>0.33</td>
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</tbody>
</table>

Fig. 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.
Table 5
95% Confidence interval of slope for 9 measurements. CI: confidence interval.

<table>
<thead>
<tr>
<th></th>
<th>BA</th>
<th>PBS</th>
<th>PAR</th>
<th>LDM</th>
<th>IDM</th>
<th>EDM</th>
<th>LSOAM</th>
<th>ISOAM</th>
<th>ESOAM</th>
</tr>
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<tbody>
<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>
</tr>
</tbody>
</table>

Table 6
Results of independent t test between automatic and manual quantifications for 9 measures, 95% confidence interval, 0.05 level.

<table>
<thead>
<tr>
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<th>BA</th>
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<tbody>
<tr>
<td>$\mu_{\text{variance}}$</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>$\mu_{\text{mean}}$</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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</table>

Fig. 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.
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. 12 shows the scatter plots and Bland–Altman plots of DM for the local centerlines, internal centerlines and external centerlines. Because the DM is 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 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 ± 1.96 \times \text{std.dev}, for internal centerline DM, 3 out of 94 centerlines are outside the range of the mean ± 1.96 \times \text{std.dev}, and for external centerline DM, 6 out of 94 centerlines are outside the range of the mean ± 1.96 \times \text{std.dev}.

Fig. 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.
Table 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 Table 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.

Fig. 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 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 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 Table 4, the correlation coefficient of SOAM between automatic and manual segmentation is close to that between manual annotations of different observers.

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 PCMRA 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 segmentation methods were optimized on 20 representative training datasets and evaluated on 76 testing datasets.

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 refinement ($\gamma$). 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. 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 (Hoogeveen et al., 1998) 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 Firouzian et al. (2010).

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 paper. 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 (Yuan et al., 1999; Ladak et al., 2001; Jin and Ladak, 2004), no evaluation for lumen segmentation (Adame et al., 2004), or evaluation has primarily focused on lumen area (Yuan et al., 1999), vessel wall area (Ladak et al., 2001) or distance between corresponding points (Jin and Ladak, 2004). 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 (Hameeteman et al., 2011). 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 ± 1.96 × 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 ± 1.96 × 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 substracting 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 lu-
men 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 paper 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. 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.

References


