Carotid plaque segmentation from three-dimensional ultrasound images by direct three-dimensional sparse field level-set optimization

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A R T I C L E   I N F O

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A B S T R A C T

Total plaque volume (TPV) measured from 3D carotid ultrasound has been shown to be able to predict cardiovascular events and is sensitive in detecting treatment effects. Manual plaque segmentation was performed in previous studies to quantify TPV, but is tedious, requires long training times and is prone to observer variability. This article introduces the first 3D direct volume-based level-set algorithm to segment plaques from 3D carotid ultrasound images. The plaque surfaces were first initialized based on the lumen and outer wall boundaries generated by a previously described semi-automatic algorithm and then deformed by a direct three-dimensional sparse field level-set algorithm, which enforced the longitudinal continuity of the segmented plaque surfaces. This is a marked advantage as compared to a previously proposed 2D slice-by-slice plaque segmentation method. In plaque boundary initialization, the previous technique performed a search on lines connecting corresponding point pairs of the outer wall and lumen boundaries. A limitation of this initialization strategy was that an inaccurate initial plaque boundary would be generated if the plaque was not enclosed entirely by the wall and lumen boundaries. A mechanism is proposed to extend the search range in order to capture the entire plaque if the outer wall boundary lies on a weak edge in the 3D ultrasound image. The proposed method was compared with the previously described 2D slice-by-slice plaque segmentation method in 26 three-dimensional carotid ultrasound images containing 27 plaques with volumes ranging from 12.5 to 450.0 mm³. The manually segmented plaque boundaries serve as the surrogate gold standard. Segmentation accuracy was quantified by volume-, area- and distance-based metrics, including absolute plaque volume difference (∆PV), Dice similarity coefficient (DSC), mean and maximum absolute distance (MAD and MAXD). The proposed direct 3D plaque segmentation algorithm was associated with a significantly lower ∆PV, MAD and MAXD, and a significantly higher DSC compared to the previously described slice-by-slice algorithm (∆PV; p = 0.012, DSC: p = 2.1 × 10⁻⁴, MAD: p = 1.3 × 10⁻⁴, MAXD: p = 5.2 × 10⁻⁴). The proposed 3D volume-based algorithm required 72 ± 22 s to segment a plaque, which is 40% lower than the 2D slice-by-slice algorithm (114 ± 18 s). The proposed automatic plaque segmentation method generates accurate and reproducible boundaries efficiently and will allow for streamlining plaque quantification based on 3D ultrasound images.

1. Introduction

Stroke is a leading cause of mortality and disability worldwide. In China, the incidence of stroke is higher than in many other countries [1]. Carotid atherosclerosis is a major source of cerebral emboli, which travel downstream and may block one of the cerebral arteries, resulting in an ischemic stroke. In asymptomatic patients with high stroke risk, monitoring the longitudinal change of atherosclerotic plaque and administering intensive medical therapy according to the amount of plaque progression have been shown to reduce the risk by 80% [2]. To manage patients’ risk in a cost-effective manner, there is an important requirement to identify the high-risk patients and target this subpopulation with intensive medical therapies. In addition, as our understanding of plaque initiation and progression mechanisms continues to advance, many new dietary/medical treatments will be developed [2]. With these improvements in treatment strategies, there is a parallel requirement for sensitive and cost-effective measurement tools for serial monitoring of progression/regression of plaque for evaluation of treatment effect.

Although ultrasound measurement of carotid intima-media thickness (IMT) has been a leading biomarker for atherosclerosis in the past 30 years, recent investigations reported that it only weakly predicts vascular events [3]. It is also increasingly clear that intima-media thickening is...
more a result of medial hypertrophy caused by hypertension, and therefore, not directly related to atherosclerosis. In addition, the duration required to detect the progression of IMT (~0.15 mm/year) does not allow for a cost-effective evaluation of new dietary and medical interventions. Direct quantification of plaque burden based on total plaque area (TPA) measurement from ultrasound images has been shown to be a stronger predictor of cardiovascular events [3,4], and be able to detect plaque change in a year [5]. 3D ultrasound measurement of total plaque volume (TPV) is much more sensitive than TPA in the detection of treatment effect. Compared to TPA, TPV has achieved an order of magnitude reduction in the sample size and duration of follow-up required to demonstrate the effects of anti-atherosclerotic therapies [6]. Wannarong et al. [3] also showed that change in TPV was a better predictor of plaque burden based on total plaque volume (TPV) is much more sensitive than TPA in the evaluation of therapies due to the inclusion of intima and media in addition to plaque [9]. Therefore, there is a critical requirement for the development of an automated and accurate plaque segmentation method.

Table 1 summarizes previously published segmentation techniques from carotid ultrasound images. The term “carotid segmentation” encompasses segmentation of the outer wall, lumen and plaque boundaries. The boundary/boundaries segmented by each algorithm was/were indicated by Y or N in this table, with Y and N standing for yes and no respectively.

Table 1

<table>
<thead>
<tr>
<th>Type</th>
<th>Paper</th>
<th>Year</th>
<th>Lumen</th>
<th>Outer wall</th>
<th>Plaque</th>
<th>Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmentation from 2D longitudinal image(s) acquired at a single anatomic cross-section</td>
<td>Rossi [10]</td>
<td>2008</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Focused on automatic recognition of the common carotid artery. No segmentation was performed.</td>
</tr>
<tr>
<td></td>
<td>Chaudhry [16]</td>
<td>2013</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Snake refinement with initial window location.</td>
</tr>
<tr>
<td></td>
<td>Santos [17]</td>
<td>2013</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Chan-Vese level-set method with lumen and bifurcation initialization based on image contrast characteristics.</td>
</tr>
<tr>
<td>Segmentation of contiguous images re-sliced from 3DUS</td>
<td>Zahalka [18]</td>
<td>2001</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Geometrically deformable models with user-selected seed points.</td>
</tr>
<tr>
<td></td>
<td>Hossain [21]</td>
<td>2015</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Distance regularized level set method with user-selected anchor points.</td>
</tr>
<tr>
<td>3D segmentation models</td>
<td>Ukwatta [22]</td>
<td>2013</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Coupled 3D level-set model anchor points on slices with preset inter-slice distance.</td>
</tr>
<tr>
<td></td>
<td>Gill [23]</td>
<td>2000</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Dynamic balloon model.</td>
</tr>
<tr>
<td></td>
<td>Solovey [24]</td>
<td>2010</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Level set method with seed points location.</td>
</tr>
</tbody>
</table>
measurements. Rossi et al. [10] developed an algorithm to recognize the common carotid artery (CCA) from a temporal sequence of 2D longitudinal ultrasound images. The authors applied a parametrical template matching technique based on the expected artery diameter range and the echo pattern of the wall-lumen complex to identify the centerline of the artery. However, the focus of this work was to recognize the common carotid artery automatically, and the authors did not attempt to segment either the vessel wall or plaque. Loizou et al. [11] segmented plaques in longitudinal images using various snake models with initialization based on Doppler flow images, and later expanded their technique to segment atherosclerotic carotid plaques from ultrasound videos of the CCA using a number of techniques including video frame normalization, speckle reduction filtering, M-mode state-based identification, parametric active contour and snake segmentation models [12,13]. Delsanto et al. [14] combined gradient-based segmentation, a snake method, and a fuzzy K-means algorithm, with an initialization based on pixel intensity to segment plaque-plus-vessel complex in longitudinal images. Destrempe et al. [15] applied a motion estimation method and a Bayesian framework to perform segmentation of plaques based on radio frequency data from longitudinal images. Chaudhry et al. [16] developed a framework to extract the intima-media complex in 2D longitudinal carotid images and then used intima-media thickness (IMT) as a feature to classify normal and diseased artery. However, the algorithm was sensitive to the orientation of the 2D longitudinal images, and control points were required from an observer to register the input image to a reference image. Santos et al. [17] used the image contrast characteristics and Chan-Vese level-set method to automatically segment the carotid lumen in 2D longitudinal ultrasound images. Since this algorithm focused only on carotid lumen segmentation, neither IMT or plaque area measurements can be made by this algorithm. This group of algorithms segmented the carotids based on an image or images scanned on the same longitudinal position, and thus, did not allow for volumetric quantification of either the vessel wall or plaque. The second type of algorithms, including Refs. 18–21, segmented the carotid vessel wall or plaque on contiguous images re-sliced from a 3D ultrasound image. Zahalka and Fenster [18] used an active contour model with user-selected seed points to segment the lumen boundary. This algorithm was validated on several phantom images. Ukwatta et al. [20] used four to six anchor points on outer wall and lumen to initialize contours and then applied the coupled level-set method to refine these contours. Cheng et al. [19] proposed an automatic algorithm for segmenting carotid plaques in consecutive 2D transverse images re-sliced from 3D ultrasound images. This work incorporated the intensity distribution and anatomical knowledge into a level-set framework and was evaluated in the CCA. Hossain et al. [21] initialized the algorithm by six user-selected points on the lumen and outer wall in seven 2D cross-sectional slices in each volume. An ellipse fitting and a stopping boundary-based energy terms were incorporated into a Distance Regularized Level Set (DRLS) framework to obtain the final segmentation results. These algorithms processed each re-sliced image individually and did not consider geometric continuity of either the vessel wall or plaque. The third type of algorithms, including Refs. 22–24, are 3D models developed for segmenting the lumen and outer
Several anchor points were required to be placed on slices with a preset inter-slice distance to form an initial surface before the coupled 3D level-set algorithm was applied. Gill et al. [23] applied a dynamic balloon model to inflate the initial lumen surface generated based on manually placed seed points within the artery. In Solovey et al. [24], markers inside the arteries were manually placed to generate the “skeleton” of the carotid lumen surface, which was then driven by a 3D active contour model according to image features and prior knowledge of arterial shape.

Although a few algorithms belonging to the first category were developed to segment plaques instead of the vessel wall, the results generated by techniques developed for plaque segmentation in 2D longitudinal images cannot be generalized to 3D ultrasound images. Unlike in 2D longitudinal images in which the propagation direction of the ultrasound beam is mostly perpendicular to the vessel wall, the ultrasound...
beam frequently travels in a direction parallel to the vessel wall interface in 3D carotid ultrasound images. We introduced the only automated algorithm for plaque segmentation from 3D carotid ultrasound images to the best of our knowledge [19]. We combined anatomical structure information and intensity information in a level-set framework to segment plaques from consecutive 2D transverse images re-sliced from 3D ultrasound images. Algorithm accuracy was evaluated only in the CCA by comparing algorithm results with manual segmentations from two experts. Although high segmentation accuracy was attained, the segmentation results were highly dependent on the accuracy of the outer wall boundaries. The outer wall boundaries used to initialize the algorithm in Ref. [19] were manually segmented. Although manual outlining of these outer wall boundaries is considered accurate and widely used as the surrogate gold standard in the evaluation of automated segmentation algorithms, the requirement of manually segmented vessel wall boundaries to initialize plaque boundaries would make a larger clinical trial laborious. On the other hand, semi-automatic algorithms, although much more efficient, may not be as accurate as manual segmentation. A limitation of the plaque initialization strategy proposed in Ref. [19] was that the accuracy of the initial plaque boundary would be greatly compromised if the segmented vessel wall (i.e., the region between the lumen and the outer wall boundaries) did not cover the entire plaque. Therefore, there is a requirement to develop and validate a plaque segmentation algorithm that could segment plaque surfaces accurately even when initialized by semi-automatically generated lumen and outer-wall boundaries.

In this work, we propose a direct 3D segmentation approach involving a number of innovations. First, we modified the plaque boundary initialization procedure to make the plaque segmentation results less sensitive to the accuracy of the outer wall boundary. This new strategy involved the introduction of a novel indicator that provided a quantitative estimation of the degree of accuracy of the outer wall boundaries at each point, and extended the search range for the initial point if the outer wall boundary was deemed not sufficiently reliable due to a weak image edge. Second, the energy functions that drove the evolution of boundary were implemented in the three-dimensional space, replacing the two-dimensional energy functions implemented for the slice-by-slice segmentation in Ref. [19]. The increased smoothness in both the longitudinal and transverse directions maintained in the proposed direct 3D plaque segmentation approach was expected to increase segmentation accuracy. Third, the proposed direct 3D plaque segmentation method was validated on the whole artery that includes the common, internal and external carotid arteries (denoted by CCA, ICA and ECA respectively hereafter), whereas the previously described method was evaluated only in the CCA. Finally, as the goal of the algorithm proposed herein is to segment plaque boundaries accurately even when initialized by semi-automatically generated lumen and outer wall boundaries, semi-automatically generated boundaries were used for plaque initialization in validation experiments, instead of manually segmentation boundaries as in Ref. [19].

Preliminary results have been previously reported in a four-page conference paper [25]. The conference paper briefly described the segmentation method and reported the segmentation accuracy in ten 3D ultrasound images. This journal paper substantially extends the conference paper, with a more comprehensive description and illustration of the algorithm, more ultrasound images for validation, and statistical tests to quantify the segmentation accuracy improvement made by the proposed 3D direct segmentation algorithm as compared to the previous 2D slice-by-slice algorithm.

2. Methods

Fig. 2 shows the workflow of the segmentation algorithm. The lumen and outer wall contours were first segmented using a previously described semi-automated segmentation algorithm [20,22]. The 3D ultrasound image was re-sliced with 1 mm inter-slice interval (ISD). An initial plaque contour was determined using an algorithm described in Sec. 2.1. A stack of plaque contours thus determined were reconstructed to a 3D plaque surface, which was subsequently deformed using the 3D level-set approach described in Sec. 2.2.

2.1. Initialization

The initialization algorithm is an improved version of a previously described algorithm [19]. We summarize the previous initialization algorithm in this paragraph and describe an issue with the previous algorithm. In the rest of this section, an approach was proposed to address the issue. In the previous algorithm, the lumen and the outer wall contours on each re-sliced transverse image were first outlined manually and were resampled, with each contour represented by 100 sample points. The resampled lumen and outer wall contours were matched on a point-by-point basis using the modified symmetric correspondence algorithm described in Chiu et al. [26], resulting in a set of correspondence lines, each of which connected a point on the outer wall and its corresponding point on the lumen boundary [blue line in Fig. 3(a)]. Then, the gray level (GL) was sampled from the lumen to the outer wall boundary along each correspondence line and subsequently fitted to a 10th-order polynomial as shown in Fig. 3(b). Local minimum points of this smoothed GL curve were identified, and the minimum point closest to the outer wall boundary was selected as the initial point. Initial points detected on each correspondence line were connected to form the initial contour.

However, the previously described algorithm is sensitive to the outer wall contour; slight inaccuracy of the contour would lead to a large deviation in plaque initialization. The first two rows of Fig. 3 show an example 2D transverse image in which the outer wall boundary fell short of enclosing the whole plaque as pointed to by the arrows. In the existing algorithm [19], the initial point was identified from a search range from the lumen boundary to the outer wall boundary along the correspondence lines. The green curves in Fig. 3(b) and (d) show the fitted GL profiles within this search range. The initial points generated based on these profiles are represented by the green asterisks in Fig. 3(a) and (c), which were located well inside the plaque. In both cases, narrowing of the search range due to a ~0.3 mm under-segmentation of the outer wall boundary resulted in a ~1.2 mm deviation of the initial point. As the accuracy of the plaque boundary generated by the subsequent level-set deformation is heavily dependent on the initial boundary, there is a requirement to generate a better initial boundary.

We introduce an approach to assess the “strength” of the outer wall boundaries, and relax the search range of the initial point at a weak image edge. The strength of the edge was quantified based on an edge map generated using a Gabor filter bank introduced previously [27]. Specifically, the Gabor filter bank consists of a set of edge-detecting filters oriented in different directions. The mother function of the two-dimensional Gabor filter bank is:

\[
g(x, y) = \frac{1}{2\sigma^2} \exp\left( -\frac{1}{2} \frac{x^2 + y^2}{\sigma^2} \right) \exp\left( \frac{2\pi i x}{\lambda} \right),
\]

which represents a 2D Gaussian function with standard deviation \(\sigma\) modulated by a sinusoid in the \(x\) direction with wavelength \(\lambda\). Filtering the original ultrasound image with \(g(x, y)\) resulted in an image highlighting the signal difference along the \(x\)-direction. To generate images that emphasize edges in other orientations, the ultrasound image was filtered by rotated versions of the mother function denoted as \(g_k(x, y)\), \(k = 0, 1, \ldots, K - 1\) and defined by:

\[
g_k(x, y) = g(x \cos k\psi + y \sin k\psi, -x \sin k\psi + y \cos k\psi),
\]

where \(\psi = \pi/K\) is the basic unit of rotation. Mehrotra et al. [28] found that the performance of the Gabor filter-based edge detector is optimized when the ratio \(\sigma/\psi\) is equal to 1/2\(\pi\), which we adopted in this study. Convolving the ultrasound image with the flipped version of each of the
K functions in the Gabor filters resulted in K filtered images $F_k(x, y) = \hat{F}(x, y) \ast \phi_k(-x, -y)$, each with an imaginary part $(\text{Imag} F_k(x, y))_{k \in \mathbb{Z}}$, representing the signal difference along one of the K orientations $(\text{Imag} F_k(x, y))_{k \in \mathbb{Z}}$. For the signal difference along the remaining K orientations within the 2x domain $\text{Imag} F_k(x, y), k \in \mathbb{Z}$, because $\text{Imag} F_k(x, y)$ is of the opposite direction to $\text{Imag} F_k(x, y)$ can be directly obtained by negating $\text{Imag} F_k(x, y)$ (i.e., $\text{Imag} F^* = -\text{Imag} F$), thus, signal difference along 2K orientations $\text{Imag} F^*_{k \in \mathbb{Z}}$ are available. In the current work, the reliability of the outer wall boundary was quantified as the signal difference along the direction $\theta = \arctan2(y - y_{center}, x - x_{center})$, where $(x_{center}, y_{center})$ is the centroid of the outer wall boundary and $\arctan2$ returns an angle within the range $[\pi, 2\pi]$. We note that a contour must be regular for its centroid to be well-defined. Although the plaque would encroach into the lumen, thereby making the lumen boundary irregular, the outer wall boundary remains circular or elliptical even with plaque encroachment [29]. For this reason, the local orientation of the outer wall boundary can be characterized based on the centroid. The metric quantifying the signal difference at the local orientation thus defined, denoted by $\hat{F}(x, y)$, was obtained by linear interpolation of the signal difference along the two closest angles (Fig. 4):

$$\hat{F}(x, y) = (1 - \beta)F_0(x, y) + \beta F_{\text{max}}(x, y),$$

where $k_0 = \lfloor \theta(x, y)/\pi \rfloor$ and $\beta = \theta(x, y)/\pi - k_0$. Fig. 5 shows imaginary interpolated images for each point $(x, y)$ on the outer wall boundary, if $\hat{F}(x, y)$ was below a preset threshold $T$, we extended the search range of the initial point outwards along the direction of the correspondence line by 0.5 mm (i.e., the new search range consisted of the original search range, which extended from the lumen to the outer wall boundaries, and the 0.5-mm segment outside the outer wall.) $T$ was chosen to be 10 gray-scale value (GSV) in this study, and this choice is supported by our previous observation [27] that the segmentation variability of the outer wall stabilized at 0.05 mm, which is a very low value, if $\hat{F}(x, y) > 10$ GSV. The red curves in Fig. 3(b) and (d) represent the fitted GL curves obtained for the extended search range. For the two example cases illustrated in Fig. 3 (a)-(d), the initial points detected from the extended range were much closer to the manually segmented plaque boundaries as labelled by the red asterisks in Fig. 3(a) and (c). The cases presented in Fig. 3 (a)-(d) represents a type of scenarios in which $\hat{F}(x, y) \leq T$. Another type of scenarios in which $\hat{F}(x, y) \leq T$ is illustrated in Fig. 3(g) and (h), in which the plaque lay close to the lumen boundary, and the outer wall boundary was not displayed clearly due to shadowing. The previously described initialization algorithm worked well in this situation, and it is important to ensure the extension of the search range introduced in this paper does not have a negative impact on the accuracy of the initial point. Fig. 3(g) and (h) show the initial points detected by the proposed algorithm in white and initial points identified by the proposed algorithm in white and initial points identified in red when the search range was extended uniformly by 0.5 mm at all locations along the boundary. The initial plaque boundaries produced by the two approaches were subsequently deformed by the level-set approach introduced in Sec. 2.2. Fig. 6(a) shows the initial points identified by the proposed algorithm in white and initial points identified in red were identified when the search range was extended uniformly by 0.5 mm at all locations along the boundary. The initial plaque boundaries produced by the two approaches were subsequently deformed by the level-set approach introduced in Sec. 2.2. Fig. 6(b) shows the plaque boundary generated by the uniform search range extension approach in green, that generated by the proposed selective search range extension approach in yellow and the manually segmented boundary in red. The initial plaque contour generated by the uniform extension approach was attracted by an edge outside the outer wall boundary, resulting in over-segmentation as compared to the manually segmented plaque boundary. The initial contour generated by the proposed selective search range extension approach was close to the outer wall boundary, and therefore, was not driven to the outside edge. The performance metrics described in Sec. 3.3 displayed in Fig. 6(b) show that the proposed selective search range approach resulted in a much more accurate plaque boundary than the uniform search range extension approach.

The initial point obtained on each corresponding line together with the lumen boundary formed a closed plaque contour on each transverse image. A stack of 2D plaque contours with ISD 1 mm obtained in this initialization process was reconstructed to produce a 3D plaque surface, which served as the initial surface for the subsequent 3D level-set evolution. Notably, the initial points were determined on each correspondence line individually without considering the continuity of the plaque geometry. The 3D level-set algorithm described in the next section incorporates a smoothness term and would smoothen the initial plaque surface.

### 2.2. 3D Level-set evolution

The sparse field level-set method [30] deformed the initial 3D plaque surface iteratively to minimize the objective energy function. The ultrasound image is denoted by $I : \Omega \to \mathbb{R}$, where $\Omega$ defines the image domain. The evolving surface is represented implicitly as the zero level-set of a 3D level-set function, denoted by $\Phi(x) : \Omega \to \mathbb{R}$, and $x \in \Omega$ is a voxel within the image domain. During the segmentation process, the function $\Phi(x)$ was iteratively evolved. Although the same set of energy functions were used to optimize the 2D slice-based segmentation technique previously introduced [19], one of the major contributions in this paper was the...
extension of these energy functions to 3D (i.e., the spatial variable $x$ in Eqs. (4)–(7) all became 3D in this paper). To the best of our knowledge, the proposed algorithm is the first direct 3D plaque segmentation method from 3D ultrasound images.

The level-set evolution process was governed by the following function:

$$\frac{\partial \Phi(x)}{\partial t} + \frac{\delta E}{\delta \Phi} \nabla \Phi(x) = 0,$$

where $E$ is the energy function described later in this section and $\frac{\delta E}{\delta \Phi}$ is the first variation of $E$ with respect to $\Phi$. $\Phi(x)$ was initialized to be the signed distance from the initial plaque surface obtained in 2.1, with $\Phi(x)$ negative if $x$ was within the plaque surface and positive if $x$ was outside the plaque surface. The energy function $E$ consists of four different terms, including the smoothness energy $E_s$, distance restriction energy $E_d$ [31], local region-based energy $E_l$ [32] and global intensity probability density function (pdf) energy $E_g$ [33]:

$$E = \lambda_s E_s + \lambda_l E_l + \lambda_d E_d + \lambda_g E_g,$$

where $\lambda_s$, $\lambda_l$, $\lambda_d$ and $\lambda_g$ are their relative weights, which were optimized according to Sec. 3.4.

$E_s$ controls the smoothness of the evolving surface and was defined as:

$$E_s = \int |\nabla H(\Phi(x))| dx,$$

where $H(\Phi(x)) = \begin{cases} 1 & \Phi(x) < -\varepsilon \\ 0 & \Phi(x) > \varepsilon \\ \frac{1}{2} \left[ 1 + \frac{\Phi}{\varepsilon} + \frac{1}{\pi} \sin \left( \frac{\pi \Phi}{\varepsilon} \right) \right] & \text{otherwise} \end{cases}$ is the regularized Heaviside function in which $\varepsilon$ is a small constant. The function
associated with green and yellow contours respectively. The metrics were defined in Eqs. (14)–(16). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 6. Example images demonstrating the advantage of the proposed selective search range extension approach for plaque boundary initialization over the uniform search range extension approach. (a) The yellow and the green contours represent the manually segmented lumen and outer wall contours respectively, and the red contour represents a contour generated by expanding the outer wall contour by 0.5 mm. The uniform extension approach searched for the initial point from the yellow to the red contour, whereas the selective extension approach extended the search range if \( F_{\text{long}} \leq 10 \text{ GSV} \). Red and white asterisks represent the initial points obtained by the uniform and selective extension approach respectively. (b) The green and yellow contours represent the plaque contours resulted from the uniform and selective approaches, whereas the manual contour is colored in red. The performance metrics displayed as green and yellow texts are the metrics surfaces. Our previous study [19] demonstrated that \( E_\text{b} \) prevented leakage of the evolving curve into plaque regions. In the current and our previous studies [19], we calculated the distances for all correspondence point pairs between the outer wall and lumen boundaries for the artery being segmented, and chose the minimum distance as \( D_{\text{min}} \).

\( E_i \) was designed to minimize the image intensity variances in regions interior and exterior of the plaque, and as a region-based energy field, is particularly useful if the plaque boundary is weak [34]:

\[
E_i = \int_B \delta(\Phi(x)) \int_{\Omega} B_i(x, \bar{x}) \left[ \left( H(\Phi(\bar{x})) (I(\bar{x}) - u_b) + (1 - H(\Phi(\bar{x}))) (I(\bar{x}) - v_b) \right)^2 \right] dx d\bar{x},
\]

where \( B_i(x, \bar{x}) = \frac{1}{\sqrt{2\pi} \sigma} \exp \left[ -\frac{\|x - \bar{x}\|^2}{2\sigma^2} \right] \) defines a Gaussian kernel centered at the voxel \( x \) with standard deviation \( \sigma \). The outer integral restricts the integration to the boundary as in Eq. (7). As illustrated in Fig. 7, the inner integral quantifies the local intensity variation inside and outside the plaque surface within a circular neighbourhood with radius \( r \) and centered at each plaque boundary point \( x \). \( u_b \) and \( v_b \) denote the mean image intensities inside and outside the plaque surface within this circular neighbourhood. The radius of this circle \( r \) determined how “local” \( E_i \) was and was selected by a parameter tuning procedure described in Sec. 3.4.

\( E_g \) measures the similarity of the intensity pdfs of regions inside and outside the plaque in terms of the Bhattacharyya distance [33]:

\[
E_g = B(\Phi(x)) = \int_{\Omega} \sqrt{P_-(\cdot|\Phi(x)) P_+(\cdot|\Phi(x))} d\zeta,
\]

where \( P_- \) and \( P_+ \) are the gray-level pdfs computed for regions interior and exterior of the plaque surface respectively. \( P_- \) and \( P_+ \) have two parameters, the gray level of the image, denoted by \( z \), and the current plaque boundary specified by \( \Phi(x) \). These two pdfs were constructed based on the gray level within the regions between the lumen and outer wall boundaries. Carotid plaques tend to have a heterogeneous texture, whereas the vessel wall consisting mainly of smooth muscle is more homogeneous. Minimizing \( E_g \) promotes the difference in the intensity profiles of the regions interior and exterior of the plaque surface, thereby facilitating the differentiation of plaques from vessel wall tissues. By taking the first variation of the \( E \) [Eq. (5)] with respect to \( \Phi \) and substituting the result into Eq. (4), the following evolving equation was obtained:

\[
\frac{\partial \Phi}{\partial t} = \frac{\delta F}{\delta \Phi} = \frac{\delta}{\delta \Phi} \left[ \int_B \delta(\Phi(x)) \int_{\Omega} \left( H(\Phi(\bar{x})) (I(\bar{x}) - u_b) + (1 - H(\Phi(\bar{x}))) (I(\bar{x}) - v_b) \right)^2 \right] dx d\bar{x},
\]
functions with standard deviations of the longitudinal continuity into account. The evolution stopped when corresponding numbers of voxels in the two regions.

3.1. Study subjects and 3D carotid ultrasound acquisition

26 subjects with carotid stenosis \( \geq 60\% \) (according to carotid Doppler flow velocities) were evaluated. These subjects were recruited from The Premature Atherosclerosis Clinic and The Stroke Prevention Clinic at University Hospital (London Health Sciences Centre, London, ON, Canada) and the Stroke Prevention and Atherosclerosis Research Centre (Robert’s Research Institute, London, ON, Canada). The study protocol was approved by The University of Western Ontario Standing Board of Human Research Ethics. All subjects provided written informed consent to this protocol.

3D ultrasound images were acquired by translating a 50 mm L12-5 transducer (ATL-Phillips, Bothell, WA, USA) along the lateral side of the patient’s neck for 4.0 cm as described in Refs. [35,36]. A linear motor assembly attached to the transducer was used to control the speed of the translation, which was set to be 3 mm/s in this study. During the translation, a video frame grabber was used to digitize the B-mode image frames obtained using an ATL HDI 5000 ultrasound machine. The acquired 2D image frames were parallel to each other with a pixel size of \( 0.1 \times 0.1 \text{mm}^2 \) and separated by 0.1 mm. These 2D images were reconstructed to a 3D carotid ultrasound image with a voxel size of \( 0.1 \times 0.1 \times 0.1 \text{mm}^3 \).

3.2. Lumen and outer wall segmentation for initialization

An expert observer blinded to the subject identity re-sliced the 3D ultrasound images with a 1 mm ISD and provided four to six initial boundaries, which was quantified by the absolute volume error \( (|\Delta PV|) \) expressed in % as defined below. For the previously introduced 2D level-set algorithm, plaque volumes were calculated for each individual plaque by multiplying the plaque area in each slice by the ISD.

\[
|\Delta PV| = \left| \frac{PV_a - PV_m}{PV_m} \right|, \tag{12}
\]

where \( PV_a \) and \( PV_m \) are the plaque volumes obtained using the automated and manual methods respectively.

Region- and distance-based metrics were evaluated on a slice-by-slice basis to offer a more detailed quantification of segmentation error. For the new algorithm in which the segmentation results were represented as a 3D surface, the surface was re-sliced transversely to generate contours on the image planes with manual segmentation for the computation of region- and distance-based metrics. The region-based metrics include absolute plaque area difference \( (|\Delta PA|) \) expressed in % and the Dice similarity coefficient (DSC) as defined below:

\[
|\Delta PA| = \left| \frac{PA_a - PA_m}{PA_m} \right|, \tag{13}
\]

where \( PA_a \) and \( PA_m \) are the plaque areas obtained using the automated and manual methods respectively.

The difference between the manual and algorithm outer wall boundaries was quantified by the mean signed distance (MSDouter), which was obtained by first matching the manual and algorithm outer wall boundaries on a point-by-point basis, taking the signed distance between the two boundaries for each correspondence pair, denoted by \( d_i \) for the \( i \)-th correspondence pair, and averaging \( d_i \) over all correspondence pairs for the two contours as expressed below. \( d_i \) is positive if the algorithm contour is outside the manual contour (i.e., over-segmentation of the outer wall by the algorithm), and negative if the algorithm contour is inside the manual contour (i.e., under-segmentation of the outer wall).

\[
\text{MSD}_{\text{outer}} = \frac{1}{N} \sum_{i=1}^{N} d_i, \tag{11}
\]

where \( N \) is the total number of correspondence pairs between the two contours.

3.3. Evaluation metrics

Segmentation accuracy attained by the proposed algorithm was compared with that attained by the previously described 2D level-set segmentation [19]. The segmented plaque boundaries obtained with the previous and current algorithms were evaluated by volume-, region- and distance-based metrics quantifying the difference between the algorithm segmented boundaries and manually segmented boundaries.

The difference between plaque volumes obtained by the manual and algorithm segmentations was quantified by the absolute volume error \( (|\Delta PV|) \) expressed in % as defined below. For the previously introduced 2D level-set algorithm, plaque volumes were calculated for each individual plaque by multiplying the plaque area in each slice by the ISD.

\[
|\Delta PV| = \left| \frac{PV_a - PV_m}{PV_m} \right|, \tag{12}
\]

where \( PV_a \) and \( PV_m \) are the plaque volumes obtained using the automated and manual methods respectively.

Region- and distance-based metrics were evaluated on a slice-by-slice basis to offer a more detailed quantification of segmentation error. For the new algorithm in which the segmentation results were represented as a 3D surface, the surface was re-sliced transversely to generate contours on the image planes with manual segmentation for the computation of region- and distance-based metrics. The region-based metrics include absolute plaque area difference \( (|\Delta PA|) \) expressed in % and the Dice similarity coefficient (DSC) as defined below:

\[
|\Delta PA| = \left| \frac{PA_a - PA_m}{PA_m} \right|, \tag{13}
\]
Table 2

Optimal parameters obtained for the previous 2D level-set [19] and the current direct 3D algorithms.

<table>
<thead>
<tr>
<th>Description</th>
<th>Parameter</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local region radius (mm)</td>
<td>r</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Smoothness weight</td>
<td>λs</td>
<td>5.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Distance restriction weight</td>
<td>λd</td>
<td>2.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Local region weight</td>
<td>λL</td>
<td>1.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Global region weight</td>
<td>λg</td>
<td>1.0</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Table 3

The means and standard deviations of the distance and area-based metrics (Sec. 3.3) for the plaque boundaries segmented using the previous 2D level-set and the current direct 3D algorithms.

<table>
<thead>
<tr>
<th>Metrics</th>
<th>2D</th>
<th>3D</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔPV(%)</td>
<td>29.7 ± 25.2</td>
<td>11.7 ± 16.1</td>
<td>.012</td>
</tr>
<tr>
<td>ΔPA(%)</td>
<td>28.4 ± 24.3</td>
<td>20.3 ± 13.5</td>
<td>.026</td>
</tr>
<tr>
<td>DSC (%)</td>
<td>760.0 ± 10.0</td>
<td>810.0 ± 6.3</td>
<td>2.1 × 10⁻⁴</td>
</tr>
<tr>
<td>MAD (mm)</td>
<td>0.43 ± 0.22</td>
<td>0.30 ± 0.13</td>
<td>1.3 × 10⁻⁴</td>
</tr>
<tr>
<td>MAXD (mm)</td>
<td>1.85 ± 1.00</td>
<td>1.39 ± 0.72</td>
<td>5.2 × 10⁻⁴</td>
</tr>
</tbody>
</table>

where PAa and PAm denote the areas of the plaque boundaries obtained using the automated and manual methods respectively.

\[
\text{DSC} = \frac{2 |R_a \cap R_m|}{|R_a| + |R_m|} \tag{14}
\]

where \( R_a \) and \( R_m \) represent the plaque regions generated by the automated and manual methods respectively and \( | \cdot | \) denotes the area of the operand.

Distance-based metrics include the mean absolute distance (MAD) and maximum absolute distance (MAXD). Boundaries segmented manually and by the algorithm were matched on a point-by-point basis using the modified symmetric correspondence algorithm [26]. Denoting the signed distance between the \( i \)-th pair of points by \( d_i \) and the total number of corresponding point pairs as \( N \) as in Eq. (11), MAD and MAXD were defined by:

\[
\text{MAD} = \frac{\sum_{i=1}^{N} |d_i|}{N}, \tag{15}
\]

\[
\text{MAXD} = \max_{1 \leq i < N} |d_i|. \tag{16}
\]

3.4. Optimization of segmentation parameters

The parameters involved in the segmentation framework \((λ_s, λ_l, λ_d, λ_g)\) and \(r\) were optimized by the Evolutionary Strategy (ES) [37] with the energy weights \(λ_s, λ_l, λ_d\) and \(λ_g\) ranging from 0 to 10, and the radius \(r\) ranging from 0.4 to 2 mm. The training data involved in parameter optimization included four 3D ultrasound images with 60 transverse slices. This dataset was excluded in performance validation. For the purpose of parameter tuning, the segmentation error was quantified by 1-DSC, where DSC is the Dice similarity coefficient defined in Eq. (14). The mean segmentation error computed over the whole set of training data served as the objective function to be minimized. We initialized ES by randomly generating 50 sets of segmentation parameters. In each ES generation, 50 sets of segmentation parameters were generated from the optimum set obtained in the previous ES generation by mutation [37], and the mean segmentation error was evaluated for each set of parameters with the set corresponding to the minimum error chosen as the optimum set in the current generation. The optimization stopped when the number of iterations reached 160.

4. Results

Examination of the 700 transverse slices from 26 carotid vessels revealed 27 plaques with volumes ranging from 12.5 to 450.0 mm³. 60 transverse slices from four 3D images were included in the training set for parameter optimization. It should be emphasized that the images involved in the training process were excluded in evaluation. Table 2 shows the optimal parameters determined for the previous 2D level-set and the current direct 3D algorithms.

Table 3 shows the means and standard deviations of the distance- and area-based metrics for plaques involved in this study. Paired t-tests show that the current direct 3D algorithm performed significantly better than the previous 2D slice-by-slice algorithm in all metrics.

Table 4 shows the area- and distance-based metrics for 13 plaques in the studied cohort. The list was sorted in ascending order of MSDouter. The proposed direct 3D segmentation method resulted in the greatest increase in DSC in Plaques 1–8 as compared to the previous 2D slice-by-slice method among the 27 plaques investigated in this study, and the DSC increase ranged from 6 to 14%. As the algorithm was motivated by adjusting the adverse effect arising from the under-segmentation of outer wall boundaries, it is not unexpected that 7 out of these 8 images were associated with outer wall boundaries that were under-segmented by the algorithm, as indicated by the negative MSDouter. The top two rows of Fig. 8 shows example axial images from 5 plaques falling into this category to illustrate the effect of the proposed approach. Each sub-figure of Fig. 8 shows two identical axial images of an example plaque with the top figure superimposed by plaque boundaries. Plaques 1, 2 and 5 shown in Fig. 8(a, b, c) were under-segmented by the previous 2D slice-by-slice method in the radial direction as compared to the manual boundaries.
The outer wall boundaries were under-segmented by 0.2–0.3 mm along these two plaques, and resulted in a ~1–2 mm of under-segmentation by the previous 2D slice-by-slice method. Plaque 6 shown in Fig. 8(d) was under-segmented by the 2D slice-by-slice method in the circumferential direction as compared to the manual boundaries, which was caused by the under-segmentation of the outer wall boundaries at locations pointed to by the arrow. Although Plaque 8 shown in Fig. 8(e) was associated with a slightly positive MSDouter of 0.02 mm, local under-segmentation of the outer wall occurred at the location pointed to by the arrow, which led to under-segmentation of the plaque by the 2D slice-

Fig. 8. Example plaques demonstrating segmentation results generated by the previous slice-by-slice method and the proposed method. Each sub-figure shows two identical images of an example plaque with the top figure superimposed by lumen and outer wall boundaries and the bottom figure superimposed by plaque boundaries.
by-slice method. In all these situations, the proposed segmentation method was able to generate more accurate boundaries as quantified by metrics listed in Table 4 through adjustment of the initial contours.

As the selected selective search range extension approach was developed to adjust for the adverse effect arising from outer wall under-segmentation, a natural question would be whether the selective extension would lower plaque segmentation accuracy if the outer wall was over-segmented. Plaques 9–13 were associated with the largest MSDouter among the studied arteries. The difference in DSC obtained in the previous and the proposed methods ranged from –1 to 3%, suggesting that the plaque contours generated in both settings were similar. This observation was confirmed by visual comparison of plaque contours shown in the bottom two rows of Fig. 8.

In our study, the expert observer took about 7 min to segment a single plaque. Using the 2D slice-by-slice segmentation method, a mean of 4.9 ± 1.3 seconds was required to segment a single image. For a typical plaque spanning a longitudinal length of 25–30 mm, slice-by-slice segmentation of a plaque with ISD 1 mm requires 114 ± 18 seconds. The direct 3D segmentation method introduced in this paper took 73 ± 22 seconds to segment a single plaque. Both 2D and 3D algorithms were executed on a single core of a 2.5 GHz PC. All algorithms were implemented using a non-optimized MATLAB (Natick, MA) implementation with occasional calls to C++ functions implementing the level-set algorithm.

5. Discussion and conclusion

The development of the automated plaque segmentation algorithm stems from the need to objectively quantify plaque volume from 3D ultrasound images for sensitive assessment of new therapies and risk stratification. Total plaque volume (TPV) has been shown to be sensitive to treatment effect [35] and a strong predictor of the combined outcomes of vascular events and death [3]. However, segmenting plaque manually from 3D carotid ultrasound images is tedious and prone to observer variability. Long training time is also required for an operator to extract plaques from the vessel wall reproducibly. To the best of our knowledge, the slice-by-slice plaque segmentation algorithm we previously developed [19] was the only algorithm available for segmentation of plaques from 3D ultrasound images. This paper extended the slice-by-slice segmentation to 3D volume-based segmentation to take into account the longitudinal continuity of the plaque. In addition, as the search range of each point on initial plaque boundary was limited by the lumen and outer wall boundaries in our previous method [19], the initial plaque contour was sensitive to the placement of the outer wall and potential inaccurate initialization had an adverse impact on the accuracy of the plaque segmentation algorithm. Fig. 3 shows that a 0.2–0.3 mm under-segmentation of the outer wall resulted in a 1.2 mm under-segmentation of the plaque. To address this issue, we proposed a more flexible strategy to determine the initial boundary of the plaque. The new initialization strategy assessed the reliability of the outer wall boundaries using the Gabor filter bank described in Ref. [27], and expanded the search range if the outer wall edge was “weak”, with weak edges defined as those associated with $F_{\text{imag}} < 10$ GSV. The threshold of 10 GSV was selected based on a previous observation that the segmentation variability stabilized at the low level of 0.05 mm if $F_{\text{imag}} > 10$ GSV [27]. Comparison of the results obtained with the previously described and the proposed algorithms shows that the flexibility introduced by the new initialization method has led to a higher segmentation accuracy as shown in Table 3. Another important advantage of the development of this 3D-based plaque segmentation technique is that the computational time required was reduced by approximately half compared to the 2D slice-by-slice technique. The increase in the computational efficiency will facilitate the translation of this technique to clinical settings.

There are several limitations in this study. Although the smoothness energy term has been widely used [19,20,22,38–40] since Chan and Vese [34] formally established its physical meaning, this energy term applies a shrinking force even after the minimum local curvature has been attained. In the absence of other forces, this term would first deform any closed surface (or contour in 2D) to a sphere (or a circle in 2D) that has the minimum local curvature. However, inward deformation would not stop here, but would continue until the circle or sphere becomes a point. This may be a factor contributing to the under-segmentation of plaques by the previous approach [19]. Although the application of another three types of forces defined in Eqs. (7)–(9) and the new selective search range extension approach did well to reduce the bias as shown in Fig. 8 and provided more accurate plaque boundaries than the previous approach, a better smoothness energy formulation should be able to reduce the local curvature without affecting regions with constant local curvatures. As an example, the smoothness force applied to a regular sphere should be uniformly zero because the surface curvatures at all points are constant. This issue has been considered in Lobertg et al. [41] in the development of the discrete dynamic contour. The authors addressed this issue by considering the point-wise curvatures in a 2D deformable contour as a discrete series and applying a filter to remove the constant component of the series. A similar approach could be adopted in 3D plaque segmentation. The deformation force at each vertex contributed by the smoothness energy can be filtered by a 2D kernel without a constant component (i.e., a spatial kernel with a Fourier transform of 0 evaluated at the frequency of 0, or equivalently, a kernel with elements summed up to 0). However, before the convolution operation is applied, 2D parameterization of the 3D surface is required, which could be achieved by constructing the area-preserving flattened map [42] we described previously for 3D carotid surfaces. The implementation and validation of this new energy term will be the focus of a future study.

The difficulty in segmenting carotid plaques accurately from ultrasound images mainly arises from their heterogeneous appearance. For example, Plaques 5 and 6 in Fig. 8 covered two echogenic regions with an echolucent region in between, and it was a challenge for the level-set algorithm to determine the circumferential coverage of the plaques. Similarly, it was difficult to determine the radial extension of Plaque 2 shown in Fig. 8. The proposed level-set deformation mechanism involved the intricate counterbalance of the smoothness energy term that penalized expansion of the plaque surface (Eq. (6)) and the global energy term that drove the plaque surface to cover all heterogeneous regions (Eq. (9)). Although a dedicated parameter tuning step described in Sec. 3.4 was involved in optimizing the weights of these energy terms, due to the small sample size available for this study and the need to reserve most arterial images for validation, only four arteries were involved in tuning the weights. A full study will be required to show how sensitive the optimized weights are to the size of the training set and the amount of improvement resulting from the use of optimized weights obtained using a larger training set.

On top of the application of the proposed automated algorithm in quantifying plaque volume for sensitive detection of treatment effect and risk stratification, the extraction of plaque textural and morphological features also requires the segmentation of plaque boundaries. Plaque echogenicity and texture characterized by carotid ultrasound have been shown to predict the combined risk of vascular events and deaths in asymptomatic patients with carotid plaques [43]. The identification of fissured or ulcerated plaques is also shown to be important in stroke risk stratification [44]. The application of the proposed 3D plaque segmentation technique obviates the need for manual plaque segmentation and allows for streamlining steps required for the extraction of these features. The segmentation approach proposed in this paper would also allow for the quantification and visualization of the spatial distribution of plaque thickness on our previously described 2D carotid maps [42,45,46]. As carotid atherosclerosis is a focal disease, being able to identify regions
where large plaque progression or regression occurs may help in clarifying how local factors, such as plaque composition, local hemodynamic factors, and local plaque morphology, affect the rate of plaque progression/regression.

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References


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