Automatic Correction of Gaps in Cerebrovascular Segmentations Extracted from 3D Time-of-Flight MRA Datasets

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Objectives: Exact cerebrovascular segmentations are required for several applications in today’s clinical routine. A major drawback of typical automatic segmentation methods is the occurrence of gaps within the segmentation. These gaps are typically located at small vessel structures exhibiting low intensities. Manual correction is very time-consuming and not suitable in clinical practice. This work presents a post-processing method for the automatic detection and closing of gaps in cerebrovascular segmentations.

Methods: In this approach, the 3D centerline is calculated from an available vessel segmentation, which enables the detection of corresponding vessel endpoints. These endpoints are then used to detect possible connections to other 3D centerline voxels with a graph-based approach. After consistency check, reasonable detected paths are expanded to the vessel boundaries using a level set approach and combined with the initial segmentation.

Results: For evaluation purposes, 100 gaps were artificially inserted at non-branching vessels and bifurcations in manual cerebrovascular segmentations derived from ten Time-of-Flight magnetic resonance angiography datasets. The results show that the presented method is capable of detecting 82% of the non-branching vessel gaps and 84% of the bifurcation gaps. The level set segmentation expands the detected connections with 0.42 mm accuracy compared to the initial segmentations. A further evaluation based on 10 real automatic segmentations from the same datasets shows that the proposed method detects 35 additional connections in average per dataset, whereas 92.7% were rated as correct by a medical expert.

Conclusion: The presented approach can considerably improve the accuracy of cerebrovascular segmentations and of following analysis outcomes.

1. Introduction

Cerebrovascular diseases such as aneurysms [1] or arteriovenous malformations [2] are a major cause for hemorrhagic strokes, which may lead to disability and death. Exact knowledge about the individual anatomy and hemodynamic situation is required for improved disease rating, therapy decision making, treatment planning and postoperative monitoring [3], especially if the disease is diagnosed at an early stage previous to rupture.

High resolution CT or MR angiographic techniques enable the clinician to obtain the required anatomical information. However, the amount of images associated with 3D angiography and the complexity of cerebrovascular systems require automatic segmentation approaches to enable fast and accurate diagnoses.

In addition, accurate vessel delineations are required for several applications such as improved visualization using surface-based rendering techniques [4, 5], finite element modeling (FEM) using computational fluid dynamics of the blood flow [6] and quantification of pathological changes associated with cerebrovascular malformations [7–9]. The segmentation of vascular structures is still of high interest and a variety of different approaches has been proposed in the past. Detailed overviews on current vessel extraction techniques are for example given by Suri et al. [10] and Lesage et al. [11].

One of the main problems of the results yielded by automatic approaches is the oc-
currence of gaps in the final vessel segmentation. In the majority of cases, these gaps are caused by low intensities in the angiographic images, which mostly occur at small vessels (Fig. 1). Small vessels may be very important, especially for planning of neurosurgeries. On the one hand, small vessels might act as feeding arteries to a vascular malformation, which need to be excluded from the global blood flow prior to surgery. On the other hand, small vessels might function as en-passage vessels, meaning that they are not directly connected to a vascular pathology but are located close to it and thus supply the intact brain tissue. Consequentially, such small en-passage vessels should not be harmed during surgery. Moreover, small vessels are also important for the planning of a vessel-free path required for brain tumor biopsies and deep brain stimulations in case of epilepsy and Parkinson disease. These examples show that even the smallest vessels might be of high interest for optimal planning of typical neurointerventions.

The problem of delineating small vessels has been addressed in several works. Passat et al. [12] discovered that only 1.44% of all automatically extracted vessels have a diameter of less than 1 mm. This finding was further confirmed by Nowinski et al. [13], who found that the sensitivity for the extraction of small vessels is as low as 16.5% and an accurate manual refinement requires about eight weeks.

Generally, it can be observed that small vessels are not missed completely by most cerebrovascular segmentation methods but are rather interrupted by numerous gaps of various lengths. Therefore, a method for the automatic detection and correction of gaps might be sufficient to detect the majority of the small vessels allowing improved overall, and especially small vessel delineation.

2. State of the Art

The number of publications dealing with the problem of detecting and correcting gaps in 3D vascular segmentations is low compared to the number of publications focusing on the general problem of globally segmenting vascular structures of various extents. Nevertheless, this problem has been addressed more frequently in 2D applications, especially in remote sensing applications, where it is, for example, required in the extraction of road networks [14].

Rochery et al. [15] used a higher-order active contour model to overcome the problem of gaps in previously extracted road maps. In contrast to this method, Tesser et al. [16] presented an approach in which the centerlines are computed and then used to define the corresponding endpoints. Endpoints located close to each other are then connected in a gap-filling algorithm if the corresponding cost functions are similar. Lacoste et al. [17] presented a gap-filling algorithm in line networks based on a global simulated annealing optimization.

A main drawback of these methods is that they were originally designed for 2D problems, and an extension to 3D is in some cases not easy to implement or not even possible from a theoretical point of view. In addition to that problem, the course of a vessel in 3D is more complex than typical roadmaps, such that the assumptions regarding the connection of endpoints are normally not fulfilled. Furthermore, these methods only focus on connecting endpoints, but in vascular segmentations, gaps might also occur at bifurcations such that a pair of endpoints is not always available.

Hassouna et al. [18] addressed the problem of detecting gaps in 3D vessel segmentation as a post-processing step in their intensity-based vessel segmentation technique. Markov Random Fields models were used to take the spatial information into account. The main drawback of this refinement method is that it can only overcome short gaps and fill holes in cerebrovascular segmentations. Another gap filling approach designed for 3D microvascular networks was presented by Risser et al. [14]. In this approach, the centerline of the segment network was computed first and then used in a tensor voting method. Although the method yields good results for small gaps, the efficiency drops with the length of a gap.

In this paper, we present an automatic post-processing method for the detection and filling of gaps of varying lengths in vessel segmentations. The proposed approach consists of four steps. Based on an existing segmentation, the 3D centerline is calculated and then used to detect the endpoints of the segmentation. In a following step, possible connections between an endpoint and each voxel part of the 3D centerline are computed using a graph-based approach using the vesselness measure as cost term. After a consistency check is performed, the detected paths are expanded.
using a level set approach to obtain the final connected segmentation.

3. Methods and Materials

3.1 Detection of Gaps and Corresponding Endpoints

The first step in the proposed post-processing procedure is to detect the gaps in existing vessel segmentations. In this approach, a gap is defined either by two vessel endpoints or one vessel endpoint and one voxel part of the 3D centerline of the cerebrovascular segmentation.

For the detection of such gaps, the 3D centerline (skeleton) of the given vessel segmentation needs to be calculated. This calculation is performed using the binary and parallel thinning method proposed by Lee et al. [19]. Here, an Euler table is derived to ensure the invariance of the Euler characteristic of the object during thinning. The algorithm has been found to be fast while at the same time achieving reliable results. Nevertheless, the method used for 3D centerline extraction can be replaced by any other method.

The extracted 3D skeleton is then used to detect the vascular endpoints. This can be performed using a voxel-wise neighborhood analysis. A vessel endpoint is defined by a centerline voxel that has exactly one neighboring centerline voxel.

3.2 Graph-based Connection of Segmentation Gaps

In our approach, a graph-based searching algorithm is used for the extraction of the course of a vessel at occurrence of a gap. This approach is motivated by the procedure of human observers, who usually follow the course of a vessel over low intensities by searching for voxels with slightly increased intensities and a typical vessel shape. Even if the vessels cannot be clearly distinguished from the background for a short distance, experienced human observers usually have the ability to ignore this problem and find a plausible path.

For the automatic connection of the extracted endpoints, a directed cost graph \( G(V, E) \) is constructed. This graph consists of a vertex set \( V \) with the vertices \( v_i \in V \) to be segmented such that \( v_i \) corresponds to voxel \( x_i \) in the image \( I(x) \) with \( x = (x, y, z) \in \Omega \) and the image domain \( \Omega \subset \mathbb{R} \). \( E \) denotes the corresponding edge set with \( (v_i, v_j) \in E \) corresponding to pairs of neighboring vertices. In this work, edges are created between the vertices of each voxel and its six direct neighbors. Finally, each edge \((v_i, v_j) \in E\) has a corresponding weight \( w(v_i, v_j) \). These weights can be defined, for example, using the intensity values of an image \( I: w(v_i, v_j) = I(x_i) \), whereas \( I(x_i) \) denotes the intensity of voxel \( x_i \).

Instead of using the intensities of a given 3D angiographic image sequence, the vesselness parameter image is used in this work to assign the weights to the edges of the graph. This vesselness parameter image can be calculated based on the original magnetic resonance angiography (MRA) image using the multi-scale vesselness filter as proposed by Sato et al. [20]. This filter assigns a value depending on a vesselness measure to every voxel, which is calculated using the eigenvalues of the Hessian matrix. This procedure leads to an enhanced display of the vascular structures, whereas the vesselness measure increases with a higher similarity to a typical tubular structure. Practically, the Hessian matrix is computed for several scales using the second derivatives of a Gaussian to enhance tubular structures of different diameters. Small scales enhance small vessels, but are also known to be more sensitive to noise. For this reason, caution is advised regarding the scales used. The computed vesselness images at different scales can for example be combined into one final vesselness image by a voxel-wise maximum operation.

Since already segmented vessel voxels are of a rather low interest for the following graph-based analysis, the vesselness parameter image is masked with the inverted vessel segmentation. The final cost image can then be calculated by inverting the masked vesselness image. The cost image is then used to assign the weights to out-edges in the graph for the corresponding vertices for each voxel. Figure 2 illustrates the images during the different stages of this pre-processing.
The problem of finding connections for the previously detected vessel endpoints can be transformed to a shortest-path problem. A path \( p \) is a sequence of vertices \( v_0, v_1, \ldots, v_k \) in the constructed graph \( G(V, E) \) such that \( (v_i, v_{i+1}) \) are in the edge set \( E \). The weight \( w \) of a path \( p \) is the sum of the weights for each edge in the path:

\[
w(p) = \sum_{i=0}^{k-1} w(v_i, v_{i+1})
\]

The shortest-path weight from vertex \( v_o \) to \( v_k \) corresponds to the path exhibiting the minimum of all possible path weights. In this work, Dijkstra’s algorithm [21] is used to find all the shortest paths from a given source to every other vertex in \( G \).

Starting with the first detected vessel endpoint, the costs of the minimal paths from the corresponding vertex \( v_l \) to all possible target vertices \( v_T = (v_{T1}, v_{T2}, \ldots, v_{TN}) \) is computed. Here, all vertices corresponding to voxels part of the previously computed 3D centerline are defined as possible target vertices \( v_T \). This approach ensures that not only endpoints can be connected to each other, but also an endpoint to a vessel, as in case of vessel bifurcations.

As a drawback, this procedure leads to the fact that most detected possible connections do not follow the course of vessel structures, but lead through non-vascular brain structures. Therefore, reasonable connections have to be separated from the remaining detected connection. For this reason, two constraints (C1 and C2) were employed in this study, which define a reasonable connection.

- **C1:** A valid connection is allowed to contain only a certain percentage \( \rho \) of voxels with a vesselness value less than \( \eta \).
- **C2:** A valid connection is allowed to contain only up to \( \lambda \) voxels in sequence with a vesselness value less than \( \eta \).

It was assumed that these two restrictions allow a successful detection of the majority of reasonable connections even over long distances while rejecting the remaining detected connections.

For reduction of the required computation time and memory for the graph-based connection of vessel endpoints to other vessels, the graph can be reduced to vertices corresponding to voxels that were classified to be brain tissue in a previously performed segmentation, for instance, using the method presented in [22].

### 3.3 Level Set Segmentation of the Connected Vessels

For expansion of the extracted paths to the vessel boundaries, a variational level set-based segmentation approach following [23] was used in this work. From a mathematical point of view, the surface of an object is expressed implicitly as the zero-level curve of the level set function \( \phi(x) \), the so-called zero level set. The optimal level set is determined by minimizing the energy functional

\[
\mathcal{J} = I + E[V, \phi],
\]

where \( V(x) \) is the preprocessed vesselness image. The functional consists of two terms: the internal energy \( I \), which is used to keep the boundary smooth and the region-based external energy term:

\[
E[V; \phi] = \int x H(\phi(x)) \cdot \log(p_{\text{inside}}(V(x))) + \int (1 - H(\phi(x))) \cdot \log(p_{\text{outside}}(V(x))) dx.
\]

Here, \( H \) denotes the Heaviside function, which is used to describe inside and outside the object. By using this formulation, available a-priori knowledge about intensity distributions \( p_{\text{inside}} \) inside and \( p_{\text{outside}} \) outside the vessels can be incorporated. Based on the known segmentation and the unprocessed vesselness image, these distributions can be estimated by sampling all intensities of the voxels part of the extracted shortest path and background voxels using a Parzen-Window strategy [24].

This leads to an iterative update scheme for the optimization of (2). For initialization of the level set segmentation, a binary image is generated from the detected paths \( p \). To prevent loss of thin structures, a dilation by one voxel is performed prior to level set extension. The level set segmentation is only used to expand the detected valid paths to the vessel boundaries while the initial segmentation is not modified. After this, the expanded paths can be combined with the initial segmentation using logical “or” combination. Figure 3 illustrates all steps of the proposed method using a synthetic software phantom.
3.4 Material and Experiments

The presented approach for the detection and filling of gaps in vessel segmentations was evaluated based on ten 3D Time-of-Flight (TOF) MRA images from patients with an arteriovenous malformation. The TOF MRA acquisition is a commonly used imaging technique in clinical practice for diagnosis of the cerebral vascular system.

The MR measurements were performed on a 3T Trio scanner (Siemens, Erlangen, Germany) using an 8-channel-phased array-head-coil, TR = 36 ms, TE = 6 ms, flip angle = 25°, 5 slabs sequence, each consisting of 40 partitions with an in-plane image resolution of 0.47 mm², slice thickness of 0.5 mm, and a FOV of 150 × 200 mm².

For each dataset, manual segmentations of the cerebrovascular system were available, which were extracted using volume growing followed by a time-consuming interactive correction in the orthogonal slices. Furthermore, automatically extracted vessel segmentations were available for each dataset, which were extracted using the multi-step fuzzy-level-set segmentation procedure described in [25] and [26].

All computations were performed on a Xeon X5400 3GHz system with 16 GB Ram and NVIDIA Quadro FX 4600 graphics card. For reduction of computation time as well as memory requirements, the graph generation was limited to a sub-volume of 75 × 75 × 50 mm³ with a given vascular endpoint defining the centre. The parameters required for the definition of valid connections were empirically defined based on one dataset that was not part of the evaluation. The parameters used in this study were as follows: \( \eta = 40 \), \( \rho = 50\% \) (constraint C1) and \( \lambda = 5 \) (constraint C2).

Three experiments were performed for evaluation of the presented method. For the first evaluation, gaps were artificially inserted into the available manual segmentations (Fig. 4). All artificial gaps were located at thin vessel structures exhibiting low intensities that were only slightly higher than the intensities of the adjacent brain tissue. It was assumed that such sites are realistic locations for gap appearances of automatic segmentations. The locations of gaps were selected manually by one medical expert by displaying the TOF MRA image sequences with color-coded overlaid cerebrovascular segmentation in the orthogonal slices. The gaps were then manually inserted at these locations using an in-house developed drawing tool. In this manor, a total of 10 gaps were artificially inserted in each dataset (100 in total), whereas five gaps were located at bifurcations and five gaps were located in the middle of a non-branching vessel (Fig. 4). The proposed method was then used to detect and correct the inserted gaps. For evaluation of the presented approach, it was analyzed how many gaps were properly detected.

In a second evaluation, the corrected gap segmentations were compared to the initial manual segmentations at the location of the artificially inserted gap. Here, the Hausdorff distance was used for quantitative evaluation of the level-set segmentation. The Hausdorff distance \( H(A_{sur}, B_{sur}) \) measures the maximal distance between the surfaces of two segmentations and is defined by

\[
H(A_{sur}, B_{sur}) = \max(h(A_{sur}, B_{sur}), h(B_{sur}, A_{sur}))
\]

with

\[
h(A_{sur}, B_{sur}) = \max_{a \in A_{sur}, b \in B_{sur}} d(a, b)
\]

Here, \( A_{sur} \) and \( B_{sur} \) represent the set of points of the two surfaces and \( d(a, b) \) the distance between two points. Low Hausdorff distances indicate a good consensus.
In the third evaluation, the automatic segmentations were used for initialization of the proposed method. After application of the presented method, a medical expert with five years of dedicated experience in neuroradiology rated the correctness of every detected and expanded path. In case of a detected and corrected gap close to the real course of a vessel, it was rated as true-positive, otherwise it was scored as a miss. Figure 3 illustrates all steps of the proposed method using a synthetic software phantom.

### Table 1

<table>
<thead>
<tr>
<th>Dataset</th>
<th>detected non-branching vessels</th>
<th>detected bifurcations</th>
<th>detected gaps</th>
<th>true positives</th>
<th>false-positives</th>
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<td>5/5</td>
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<td>2/5</td>
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<td>4/5</td>
<td>51</td>
<td>47</td>
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</table>

Overall: 41/50 = 82% 42/50 = 84% 346 321 25

### Results

Table 1 shows the evaluation results from the proposed post-processing approach for automatic gap correction. The results of the first evaluation using the manual segmentations with artificially inserted gaps revealed that 83% of the inserted gaps were detected and proper paths reconnecting the vessel endpoints to a vessel endpoint or vessel were found. The results were further sub-divided with respect to the style of the gap inserted. The results of the gap filling for the gaps inserted at bifurcations are nearly equal (42 of 50 gaps are correctly connected) to the results regarding gaps located at non-branching vessels (41 of 50 gaps are correctly connected). One of the bifurcation-gaps rated as not-properly detected was connected to only one of the two side branches. The remaining not-detected bifurcation gaps were missed completely. The artificially inserted gaps used for the first two evaluations had a mean length of 7.15 mm (min: 3.67 mm; max: 18.94 mm). No significant correspondence between gap detection and length of gap was found. This finding may be ascribed to the fact that the gap closing was only executed in rather small sub-volumes, which limits the maximal length of possible vessel paths. However, the usage of larger sub-volumes may have an increasing effect on the detection rate of longer gaps as the two constraints are more likely to get violated.

The quantitative results from the second evaluation using the Hausdorff-distance measure suggest that the proposed level set segmentation procedure is capable of dilating the detected paths to the vessel boundary. Overall, a mean Hausdorff distance of 0.42 mm was achieved comparing the level-set segmentation with the manual segmentation prior to gap insertion, which is in the range of the voxel size of the analyzed data-sets. Gaps that were not detected by the graph-based approach were not included in this evaluation. A visual inspection of the gap correction results reveals that the level set extension leads to slightly thicker vessels compared to the manual segmentation (Fig. 4), which leads to Hausdorff distance of 0.42 mm. This problem can be ascribed to indirect Gaussian smoothing applied for vesselness parameter image calculation.

The results of the third evaluation using the automatically extracted segmentations show that 346 gaps were detected and corrected by the proposed method in the 10 datasets (average = 35). 321 of these 346 gaps were rated as correct by the medical expert and 25 were judged as false-positives; thus, the proposed method yields an accuracy of 92.7%. The false-positive connections can all be ascribed to locations where two or more vessels are located very close to each other. More precisely, this problem only occurred if two vessels were so close to each other that the constraint C2 was not violated.
The artificially inserted gaps used for the first two evaluations were short in contrast to connections detected in the third evaluation using the automatic segmentations for initialization. Visual measurements revealed that the proposed method is able to detect even very long connections up to 5 cm (Fig. 5). It should be mentioned that no evaluation regarding non-detected (false-negative) gaps was performed, as this is a very difficult task for visual rating. However, visual rating revealed that most of the clearly visible vessels and gaps were detected by the proposed method.

5. Discussion

The detection and closing of gaps in vascular segmentations is important for several applications dealing with vascular systems. In this paper, an automatic post-processing method for the detection and filling of gaps in vessel segmentations was presented.

The proposed approach was successfully applied to ten clinical TOF MRA datasets of patients with an arteriovenous malformation (AVM). It should be emphasized that the presence of AVMs in the datasets did not influence the results of the presented method, as these pathologies are represented by enlarged vessels with high intensities and were sufficiently delineated in the initial segmentations.

The evaluation and visual inspection revealed that the proposed approach can detect and reduce gaps in vascular segmentations and can therefore enhance the accuracy of the extracted vascular system. The accuracies for the detection of gaps at bifurcation and non-branching vessels were nearly identically. Due to the fact that bifurcations do not exhibit a typical vessel shape, reduced vesselness values can usually be observed at these branching points. Therefore, lower accuracies for the correction of bifurcation gaps might be expected. However, our evaluations have shown that the proposed method is able to overcome this problem, which can be ascribed to the two constraints used for definition of valid paths and find reasonable connections.

Still, more datasets have to be evaluated to validate the quality of the presented method. Apart from application to more TOF MRA datasets, it is planned to apply the presented method to MRA and CTA datasets of different vascular systems (e.g. the liver) to evaluate the broader application opportunities of this approach.

The parameters used for definition of a valid connection have only been estimated empirically and might not yet reflect the optimal choice. Therefore, a quantitative analysis of the impact of these parameters might lead to improved results of the proposed gap correction procedure in terms of more corrected gaps. However, this might also lead to more occurrences of false-positive connections, which has to be evaluated at the same time when optimizing the parameters. Such a quantitative analysis will be time-consuming as complex visual ratings are required for this.

Furthermore, it might be valuable to extend the proposed method by the direction information that can be derived from the vesselness filter. This strategy might allow a reduction of the number of false-positive connections occurring if two vessels are located very close to each other. However, the found false-positiv connections are not really severe for most clinical applications. For example, when planning a vessel-free path it is very unlikely that clinicians decide for a path, which leads through the space between two vessels that are located very close to each other. Nevertheless, if these false-positives are important for clinical decisions, the time required for manual correction will be considerably lower compared to manually delineating small vessels as these false-positive connections are locally restricted to the space between two close vessels.

Self-evident, the number of connections found depends to a large extent on the initial cerebrovascular segmentation used for post-processing. Due to the fact that the initial automatic segmentations used for the third evaluation already cover the majority of small vessels, more connections should be found in segmentations that cover less small vessels. Therefore, it might be interesting to compare different segmentations results before and after applying the proposed method as a reduction of variances might be expected.

It has to be emphasized that the proposed method is computationally expensive, which can be ascribed to the shortest path tree calculation using Dijkstra’s algorithm. Figure 6 shows the dependency between the sub-volume size and the required calculation time including graph construction, shortest path detection and saving the detected paths. Here, it can be

<table>
<thead>
<tr>
<th>Sub-volume size (in mm³)</th>
<th>Computation time for one vessel (in sec)</th>
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<tbody>
<tr>
<td>0</td>
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<td>10</td>
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**Fig. 6** Average required calculation times for one vessel endpoint and different isotropic sub-volume sizes.
seen that the calculation time required for one vessel endpoint increases nearly exponentially with the size of the analyzed volume. As analyzing the whole image volume would be computational very expensive, only sub-volumes were used for the graph generation as described in the Experiments section. The results of the experiments suggest that the used sub-volume size of 75 × 75 × 50 mm³ is reasonable for the detection of most gaps. However, more experiments are necessary to estimate the optimal sub-volume size. With the present sub-volume size and voxel spacing of the TOF datasets, the average time required for graph construction and Dijkstra calculation for one vessel endpoint is approximately 12 seconds for a typical dataset as used in this study. Therefore, the graph-based connection of a typical dataset requires about 60 to 90 minutes per dataset on a typical multi-core system as used in this study, including all preprocessing steps and level-set based post-processing. Nevertheless, surgery planning of unruptured vessel pathologies and definition of vessel-free paths as required for brain tumor biopsy and deep brain stimulation is usually not critical in terms of time. Compared to several hours of manual post-processing, the proposed method still appears reasonable for clinical applications especially since no manual interaction is required.

Furthermore, it has to be emphasized that the presented method assumes that a proper initial segmentations is given. Therefore, a previous consistency check regarding the plausibility of the initially segmented vessel structures might be a valuable extension to this method. Otherwise, the results of the gap closing may not be satisfying in case of incorrect initial segmentation results, especially in the case of overestimating false-positives.

In conclusion, the presented approach can considerably improve the accuracy of a given cerebrovascular segmentation and the outcome of following analysis steps. Furthermore, the presented approach is independent of the previous segmentation method, since the cost function can be exchanged easily. In the case of previous intensity based segmentation, the edge weights can be defined using a shape-based measure. Alternatively, shape-based segmentations can be refined using intensity-based cost terms.

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References