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Abstract. Vascular segmentation plays an important role in the assessment of peripheral arterial disease. The segmentation is very challenging especially for arteries with severe stenosis or complete occlusion. We present a cascading algorithm for vascular centerline tree detection specializing in detecting centerlines in diseased peripheral arteries. It takes a three-dimensional computed tomography angiography (CTA) volume and returns a vascular centerline tree, which can be used for accelerating and facilitating the vascular segmentation. The algorithm consists of four levels, two of which detect healthy arteries of varying sizes and two that specialize in different types of vascular pathology: severe calcification and occlusion. We perform four main steps at each level: appropriate parameters for each level are selected automatically, a set of centrally located voxels is detected, these voxels are connected together based on the connection criteria, and the resulting centerline tree is corrected from spurious branches. The proposed method was tested on 25 CTA scans of the lower limbs, achieving an average overlap rate of 89% and an average detection rate of 82%. The average execution time using four CPU cores was 70 s, and the technique was successful also in detecting very distal artery branches, e.g., in the foot. © 2017 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: [10.1117/1.JMI.4.2.024004](https://doi.org/10.1117/1.JMI.4.2.024004)]

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1 Introduction

Peripheral arterial disease (PAD) is an important health problem, particularly in developed countries. It is a frequent disease, most commonly caused by the pathological process called atherosclerosis. In this process, a plaque, which may contain fat, cholesterol, fibrous tissue, and calcium, builds up in the wall of an artery. Over time, the plaque causes narrowing of the artery lumen until it completely blocks the artery. This limits the flow of oxygen-rich blood to the organs, particularly in the lower extremities.

For many years, invasive digital subtraction angiography (DSA) was considered the standard technique for assessing PAD. However, the development of new computed tomography (CT) hardware has made multidetector computed tomography angiography (CTA) an effective alternative to DSA.¹ Just like with DSA, the method requires an iodinated contrast agent and ionizing radiation, with potential adverse effects to the patient; however, no arterial injection is needed, which reduces complication risks considerably. In addition, multidetector CTA provides high resolution, nearly isotropic volumetric images that permit seeing the patient's anatomy from multiple angles. The CTA imaging provides helpful information for doctors to assess PAD morphology, and it reveals the presence of stenosis. Image analysis plays an important part in the evaluating process, especially a vascular segmentation. The vascular segmentation is

needed for quantitative measurements (e.g., vessel diameters, areas, or volumes) that help the doctors to decide whether to perform an intervention or to assess the efficiency of the provided therapy.

Diseased arteries with severe stenosis or complete occlusion represent the greatest clinical interest. However, these are also where the segmentation methods tend to have most difficulties. Challenges are due to the narrow, irregular lumen, intensity variations along the arteries caused by stenosis or calcification, and often incomplete contrast filling. A phenomenon that may occur in diseased cases is the appearance of collateral arteries, i.e., smaller vessels offering an alternative route to the flowing blood, which are normally invisible but may dilate to compensate for the impaired flow in the larger artery. These vessels, which tend to have a tortuous and irregular course, are typically difficult to handle for current segmentation algorithms. In late stages, atherosclerotic plaques often contain calcifications. Due to their high radiopacity, the calcifications may confuse a segmentation algorithm adapted to lower intensities in the arterial wall not the contrast-filled lumen.

One way to address different vascular pathology challenges is to devise a cascading algorithm that works at several levels, where each level is specialized for detecting a different type of vascular pathology. In this paper, we propose such a cascading algorithm for vascular skeleton extraction. In our case, the vascular skeleton is intended to be the first step of a complete arterial tree segmentation. By first identifying the vascular

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skeleton and then performing the segmentation step, we can facilitate and accelerate the whole segmentation process. This is important since the steadily increasing resolution of volumetric images tends to put higher and higher demands on the performance of image analysis techniques. The proposed algorithm builds on our previous work,² but we expand the algorithm and focus on the diseased peripheral arteries. The first two levels are similar to the ones we have presented in our previous work. The contribution in this study lies in the other two levels that solve challenging situations where the previous method failed. The output of each level is a portion of the vascular skeleton, and this is cumulatively added together to form the skeleton of the whole vasculature as a final product. The subsequent segmentation step is then based on a level-set propagation from the obtained vascular skeleton. The level-set-based segmentation algorithm was presented in Ref. 3. In that paper, however, the vascular skeleton extraction was based on a semiautomatic, relatively time-consuming approach.

Our method provides a rough vascular skeleton extracted fully automatically and time efficiently from healthy and diseased arteries, which opens the possibility of using it clinically without disturbing delays. In combination with the segmentation algorithm presented in Ref. 3, the whole framework is able to provide a precise vascular segmentation of the lower limbs, which is very valuable for clinical evaluation of the state of the diseased arteries.

2 Previous Work

In recent years, segmentation of blood vessels has become a popular research topic that attracts many researchers. This attraction has resulted in rapid development of a wide range of methods for vascular segmentation. In Sec. 3, we discuss some of the popular vessel segmentation techniques and focus mainly on papers dedicated to segmentation of diseased, small arteries, or peripheral arteries. Further, we also mention some previous work on skeleton-based methods, which are the methods that first extract the vascular skeleton from medical images and subsequently detect the vascular walls. A more comprehensive review on vascular segmentation techniques is presented in Refs. 4–6.

One of the most popular approaches for vessel segmentation is based on a region growing process originating from automatically generated or user-defined seed points.⁷ This algorithm is simple and can produce well-defined object boundaries as long as the object intensities are homogeneous. Vascular structures, however, are long and narrow, and even a slow variation in their intensity can stop the region growing. To compensate for this problem, a locally adaptive region growing algorithm was proposed by Yi and Ra.⁸ This algorithm is based on local cube tracking where the intensity threshold is adapted for each current local cube separately using the cost function calculated along a path connecting the previous cube's seed point and each of the current cube's voxel. However, even such a compensation is often not enough to avoid failing once the blood artery is partially or completely occluded or to stop the growing due to noise and partial volume artifacts in small and narrow arteries. Another disadvantage of conventional region growing is low computation efficiency and large memory usage, especially for three-dimensional (3-D) images. A method proposed by Ye et al.⁹ introduced a nonrecursive single-pass region growing to overcome this issue.

Other popular segmentation algorithms are based on a tracking approach. The vessel tracking approaches usually start from an initial point, analyze the local neighborhood voxels lying orthogonal to the tracking direction, track the vessel centerline, and finally detect the vessel borders. Wink et al.¹⁰ introduced such a method where the vessel centerline and the vessel surface are tracked concurrently. The method starts from two user-defined points, where the first point specifies a starting position and the second point gives an initial tracking direction. This method successfully applies to vessels with varying width and is robust to typical vascular perturbations, such as calcifications in CTA images.

Another tracking method proposed by Wink et al.¹¹ uses an extension of the minimum cost path search between two seed points. The method propagates the wave front through a vectorial multiscale feature image and is, therefore, more inclined to follow a vessel of similar size than of similar intensity. This property makes the method more robust to overlap and to the presence of adjacent structures, and it also has a potential to cope with severe stenosis. Similarly, another method presented by Li and Yezzi¹² also uses a minimal path algorithm in one higher dimension to obtain a direct representation of vessel surface between two points. This method is able to reconstruct tubular structures from noisy and low contrast data. None of these methods, however, are suitable for full vascular tree centerline detection since they can track only a single vessel and cannot handle topological changes during the tracking. A method that uses the minimum cost path and at the same time is able to detect the full vessel centerline tree was presented by Gülsün and Tek.¹³ The algorithm starts from a single seed point and uses multiscale medialness filters to extract the multibranch centerlines. Providing a single seed point should be sufficient in cases of healthy vessels. In the presence of total occlusion, however, another seed point on the other side of the occlusion must be used. Another algorithm that is topologically adaptable was recently proposed by Zhu et al.¹⁴ In this algorithm, the skeleton tree is first modeled as a collection of single centerlines originating from one common center node leading to each vessel branch. Such a star network contains many redundant skeleton points and therefore is cleaned and reconfigured using morphological operations into the final skeleton tree.

One of few papers that focuses on detecting small 3-D vessel structures in CTA data also uses a vessel tracking approach.¹⁵ The authors introduce a specific vessel template model that is analytically fitted to the image data. This method is able to simultaneously track multiple hypothetical vessel trajectories while traversing low contrast passages. For the model to fit the vessel successfully, the vessels should have bright intensity on a darker background, and there is no need to specify an expected vessel intensity range. This is an advantage as it enables users to use the method without knowing the absolute vessel intensity. The only input needed for running the method is at least one seed point. A disadvantage of the method is that the detection may unintentionally jump from vessels to bones. These errors occur because the detection is based on following structures that are morphologically similar to vessels and not based on intensity.

Applying vascular segmentation to peripheral arteries afflicted by arterial occlusive disease often results in gaps or discontinuities. Several methods focusing on reconnecting the gaps have been proposed. An iterative tensor voting strategy for identifying curvilinear structures in two-dimensional (2-D) images,

primarily from microscopy, was introduced by Loss et al.¹⁶ However, it only applies to relatively small gaps. Bates et al.¹⁷ presented a strategy where they combine both skeleton- and intensity-based information to fill large discontinuities. Since the main goal of this method is to fill gaps originating from thresholding the vesselness likelihood map, the method may not be suitable for detecting collateral arteries. In general, the collateral arteries branch out from the occluded artery far from the place where the occlusion starts, contrary to what methods for gap filling usually assume.

Our previous work² extracts a vascular centerline tree from the CTA images. It was tested on datasets of the lower limbs taken from clinical routine; however, it was not designed to find connections between vascular skeleton segments. The two main problems were vascular occlusion and severe calcification in the vessel wall. A severe calcification can be recognized on the CT scan by the presence of very bright intensities inside the arterial lumen, usually affecting both sides of the lumen. Vascular occlusion can be recognized by the sudden disappearance of the vessel, often even at lengths of several centimeters. Since different vascular pathologies have different appearances on the CT scan, we propose a cascading algorithm to overcome this problem. Each level in the cascade detects different appearance and contributes by partial results to the final vascular centerline tree. This brief review of previous work showed the need for a vascular segmentation or skeletonization method that would perform well on diseased peripheral arteries and at the same time be fast enough for clinical use. Our proposed algorithm offers a possible solution to this need.

3 Proposed Method

The proposed method builds on our previous work.² However, we expand it to solve challenging situations where vascular occlusion and severe calcification are present in the arteries. We will give a brief outline of the parts that are similar to the previous work and describe the newly added parts in depth to give the reader the whole image of the process. An outline of the proposed algorithm is presented in Fig. 1.

The method for vascular skeleton tree extraction takes a 3-D unprocessed CTA scan as an input and produces a graph as an output. This graph is represented by nodes and edges, where nodes are voxels located in the middle of the artery and edges are connections between them passing along the artery. The input data are processed in several levels (represented by rows in Fig. 1), where each level specializes in extracting centerlines of different kinds of arteries. By different kinds, we mean arteries of different sizes (large and small) or different pathologies (calcification and occlusion). The centerlines produced at each level are cumulatively added together, forming a complete vascular centerline tree. Both the first- and the second-level detect centerlines of healthy arteries or arteries contain only light calcification. The first level focuses on large arteries, and the second level aims to detect small artery centerlines. The subsequent levels focus on diseased vessels, where each level specializes in a different pathology. In this work, we propose a level that focuses on arteries that contain severe calcifications and another level that aims to detect centerlines of tiny arteries in the lower extremities and collateral arteries that grow when part of the main artery is occluded by plaques.

Fig. 1 Flow chart of the proposed method. The first row introduces four algorithm steps together with the image pictograms explaining what is done in each step. The first column introduces four algorithm levels together with an image example showing vessel types detected at each level. From the upper left corner, the input 3-D volume is processed through all four steps of the first level and then all four steps of the second, third, and fourth level, forming the skeleton of the whole vasculature as a final output. Illustrations in black boxes show a contribution of each level and step. Green (bright) or red (dark) color in the boxes represents nodes or connections that were added or removed at that particular point in the process, respectively.

At each level, four main steps are performed (represented by columns in Fig. 1). The parameter selection step automatically sets proper intensity ranges for different anatomy structures based on histogram analysis and load parameter values needed for this particular level. In the node detection step, different filters are applied to the data to select a set of voxels, located centrally within the artery cross section. The design of the filters is based on intensity, size, and shape analysis of elliptical cross sections of arteries on 2-D planes. The node connection step connects nodes using the distance and intensity information, thus creating a centerline tree for the entire vasculature. The last anatomy-based analysis step corrects the resulting centerline tree and cleans it from spurious branches based on their shape and size.

3.1 Steps of the Method

In this section, we focus on the individual steps of the proposed method. We briefly clarify each of the main steps and reveal values for the parameters that detect centerlines of different kinds of the vasculature.

3.1.1 Parameter selection

The main task of the parameter selection step is to set proper parameter values needed for the algorithm to run. Depending on whether the parameter value changes for each input volume or stays fixed, each parameter can be classified into one of two parameter groups.

“Changeable parameter group” gathers parameters whose values depend on the input volume and are calculated from the intensity histogram. The intensity histogram analysis tells us which intensities correspond to important tissue classes, such as fat, muscle, and blood for each particular volume. In CT, the voxel intensity is expressed in Hounsfield units (HU). While for tissues, such as muscle and fat, the intensities are standardized among different CT machines, the intensity value of blood with injected contrast medium is not constant, can vary between the scans, and therefore needs to be measured. The variation is caused mainly by different hemodynamics in each patient and time differences between injection and image acquisition. An automatic algorithm proposed in Ref. 2 fits Gaussian curves to the smoothed image histogram of CTA data and returns the intensity ranges for three important anatomical tissue types: fat $[\theta_{\text{low}}^f, \theta_{\text{high}}^f]$, muscle $[\theta_{\text{low}}^m, \theta_{\text{high}}^m]$, and blood $[\theta_{\text{low}}^b, \theta_{\text{high}}^b]$.

Parameters in the “fixed parameter group” are well defined for each algorithm level and have the same value for all input volumes. All fixed parameters with their corresponding values for each algorithm level are listed in Table 1. In brief, the minimum and the maximum radius parameters [min_radius, max_radius] specify the size of the arteries we aim to detect at each algorithm level. Arteries usually do not have diameters >50 mm, so the overall upper limit for max_radius is 25 mm. The overall lower limit for min_radius is limited by the size of the voxel in the database. Gradient_thresh parameter sets a threshold on the smoothness of the perimeters of the elliptical cross sections that we are interested in detecting. Large arteries, such as the aorta and its main branches, often have more uneven elliptical cross sections compared to smaller vessels, which maintain their shape and have smooth and regular cross sections. We use a measure to calculate the smoothness that ranges from 0 to 1, where 0 represents an ideal ellipse and 1 reflects very uneven perimeter of a cross section. This parameter is used in the node detection step. The parameter max_edge_length is applied in the node connection step and limits the maximum length of the edge between two nodes. The parameter cutting_thresh sets a threshold for cutting off short branches (pruning). As arteries can have small bulges or irregularities in shape, some nodes are detected inside these bulges close to the arterial wall. In the node connection step, these nodes are connected to other nodes, forming short spurious artery branches that should be removed. Two final parameters are angle_thresh and long_graph_thresh. Both are applied during the anatomy-based analysis. The parameter angle_thresh specifies the minimum allowed average angle per branch, and the parameter long_graph_thresh defines the minimum axial length of the graph. These parameters eliminate false artery graphs detected in anatomical structures that resemble the arteries in terms of intensity and cross-sectional shape.

3.1.2 Detection of nodes

In the node detection step, the volumetric CTA data are scanned through all planes in three different orientations: axial, sagittal, and coronal. Within each plane, we are interested in voxels that have intensity within the blood intensity range as these voxels might represent the vascular structure. In addition, if such a voxel is centrally located in an area of other voxels having intensities from the same range, it is added to a set of potential

Table 1 Fixed parameters used in the algorithm listed with their corresponding values.

Parameter name	Applied in step	Value used in first level	Value used in second level	Value used in third level	Value used in fourth level
min_radius	Node detection	2 mm	Limited by the voxel size	2 mm	Limited by the voxel size
max_radius	Node detection	25 mm	2.5 mm	25 mm	1.5 mm
gradient_thresh	Node detection	0.6	0.4	0.6	Not used
max_edge_length	Node connection	70 mm	35 mm	70 mm	10 mm
cutting_thresh	Node connection	Three times the radius of the artery at a bifurcation point			
angle_thresh	Anatomy-based analysis	$3\pi/4$ rad			
long_graph_thresh	Anatomy-based analysis	1/15 of the leg length	1/7 of the leg length		

node voxels. However, other structures, such as trabecular bone tissue, bone surface, or beam hardening artifacts, also have intensities within the blood range and therefore the description based on intensity is not sufficient. The potential node voxels need to be further examined by a set of filters and removed from the set if they do not fulfill all filtering criteria. The filters examine the potential node voxel together with voxels on the perimeter of three ellipses centered around the node. All three ellipses are concentric and lie in the same plane. An ellipse that limits the area of blood intensity voxels is called bounding ellipse. The remaining two ellipses are named inner and outer ellipse. The size of the bounding ellipse is determined by a sudden intensity difference detected along four rays cast into four main directions (with the angular difference of 90 deg) from the potential node. The inner and the outer ellipse have 1.5 mm shorter and longer axes, respectively, than the bounding ellipse. The filters for removing false artery nodes are

1. $I_{\text{avg}}^I \in [\theta_{\text{low}}^b, \theta_{\text{high}}^b]$, where $I_{\text{avg}}^I = \frac{1}{N} \sum_{n=1}^N I_n^I$ is the average intensity of N voxels from the perimeter of the inner ellipse.
2. $I_{\text{min}}^O \wedge I_{\text{max}}^O \in [\theta_{\text{low}}^f, \theta_{\text{high}}^f]$, where $I_{\text{min}}^O = \min \{I_n^O\}_{n=1}^N$ is the minimum intensity and $I_{\text{max}}^O = \max \{I_n^O\}_{n=1}^N$ is the maximum intensity of N voxels from the perimeter of the outer ellipse.
3. $\Gamma^B \leq \text{gradient_thresh}$, where $\Gamma^B = |\frac{1}{N} \sum_{n=1}^N \nabla_n^B|$ is the magnitude of the averaged local gradient vectors normalized to the maximum gradient on the voxels from the perimeter of the bounding ellipse.
4. $a \leq \text{max_radius}$ and $b \leq \text{max_radius}$, where a and b are the major and the minor axes of the bounding ellipse, respectively.
5. $a \geq \text{min_radius}$ and $b \geq \text{min_radius}$

All voxels that successfully pass through the filters are saved as artery nodes together with their respective position and radii. The radius r for each node is calculated using an area-preserving transformation from an ellipse to a circle $r = \sqrt{ab}$.

3.1.3 Connection of nodes

In the node connection step, the detected nodes are linked together based on a set of connection criteria. In the first level, each node is a separate graph. Starting with these separate graphs, we gradually add new connections. A link from node A in graph G_A to node B in graph G_B can be established only if all the following connectivity conditions are satisfied:

1. $G_A \neq G_B$.
2. Node B has a bigger or equal radius to node A .
3. Every voxel on the link from A to B has an intensity from the range $[\theta_{\text{low}}^b, \theta_{\text{high}}^b]$.
4. The distance between node A and node B is less than max_edge_length .
5. There is no other node C for which the Euclidean distance between nodes A and C is shorter than between nodes A and B that fulfills conditions 1 to 4.

Graphs built at the previous levels within the algorithm are connected with the newly detected nodes from the current level, and connections among the newly detected nodes themselves are established, creating one or more centerline trees. From each centerline tree, all branches shorter than cutting_thresh are removed. Removing short branches will clean the graph from spurious branches created by connecting nodes detected in bulges and irregularities close to the artery surface.

3.1.4 Anatomy-based analysis

To distinguish between true and false artery nodes, the graph geometry is analyzed. False artery nodes are detected in anatomical structures that resemble the arteries in terms of intensity and cross-sectional shape. For CTA images of the lower limbs, these false nodes are detected in bone surfaces of knee or pelvis region where they connect into zigzagged graphs and accumulate in a blob-like—random—structure. True artery nodes, on the contrary, connect into a sequence and create line structures. An angle between two edges in the true artery branch, on average, is not far from the straight angle (π rad). Graph segments with the averaged sum of absolute angles per branch under angle_thresh will be removed. All graphs for which the axial length is longer than long_graph_thresh will be kept. Last, those of the remaining graphs that do not have a connection with the graph produced by the previous levels are also removed. After the last step of the last level, a skeleton of the whole vasculature is created.

3.2 Levels of the Method

In this section, we explain all the necessary changes among the individual levels, which allow the centerline detection of different kinds of the vasculature.

3.2.1 Skeleton of large arteries

In the first level, the algorithm focuses on extracting a skeleton of large and healthy arteries. All parameters are therefore set to detect large arteries: the aorta and its main branches. The fixed parameter values used in this level are reported in Table 1, and the changeable parameter values were automatically set by applying a Gaussian curve fitting algorithm to the volume histogram. All steps are performed as described earlier.

The first level is important since the graph produced by this level serves as a base for distinguishing between true and false artery graphs or graph segments in the next levels. Therefore, in the first level, the algorithm is more strict to remove all false artery segments even at the price of removing true artery segments. It is possible that the removed true arteries from this level will be added back in one of the later levels when the criteria for removal are less strict.

3.2.2 Skeleton of small arteries

This level specializes in detecting a centerline of healthy arteries that have smaller diameters. Here, we set the threshold between bigger and smaller arteries to radius 2.5 mm; however, it is possible to adjust the parameter to the application. The main difference in the second level compared to the first level is the set of fixed parameters (see Table 1). Regarding the changeable parameters, the lower bound of blood vessel intensity range needs to be lowered by 10% of the muscle intensity range [see Fig. 3(c)] and is therefore temporarily reset to $\theta_{\text{low}}^b \text{ new} = \theta_{\text{low}}^b - 0.1 * (\theta_{\text{high}}^m - \theta_{\text{low}}^m)$.

This is motivated by the partial volume effect, where the narrow and small vessels tend to have a lower intensity than the large vessels. All algorithm steps are performed as described earlier. However, for detecting vessels with a diameter down to the range of a single voxel, filter nos. 1 and 3 are skipped as the bounding and the inner ellipses are too small in such narrow arteries.

3.2.3 Skeleton of arteries with severe calcification

In the third level, the algorithm focuses on detecting artery segments containing severe calcifications. The lumen of these arteries contains blood that may be surrounded by calcium that has accumulated in advanced plaques. Blood has intensities as calculated in the parameter selection step by analyzing the intensity histogram. However, calcium has much higher intensities exceeding the predefined blood intensity range [Fig. 2(a)]. The previous levels did not extract a centerline from such diseased artery segments because either the calcification was so strong that no potential node was detected in that region [see the left large artery cross section in Fig. 2(b)], or calcification was present in the vessel wall. In this case, the basic criteria were fulfilled and a potential node was detected, but the potential node did not pass through the set of filters as the intensities on the outer ellipses were too high [see the right large artery cross section in Fig. 2(b)]. To avoid this problem, the blood vessel intensity range at this level is temporarily reset to values $[\theta_{low}^b, \text{max intensity}]$ [Fig. 2(c)]. By updating the predefined blood vessel intensity range to these new values, both blood and bone intensities are included in the range. Therefore, elliptical cross sections of anatomical tubular structures, such as arteries, bones, or calcified arteries, will be detected. A high number of false nodes will be found inside the bones; however, these nodes will not be connected to the trustworthy set of centerlines obtained in the first level, and therefore they will be removed.

3.2.4 Skeleton of minute collateral arteries

The last level extracts the vascular centerline of tiny collateral arteries. The skeleton of these thin vessels is needed in cases where the lumen of the artery has been completely occluded by an atherosclerotic plaque. Since no blood mixed with the contrast agent was present inside this artery segment during the image acquisition, the segment is invisible in the CTA images. However, if the contrast medium reaches the distal part of arteries, then there has to be a connection through smaller

arteries that dilated overtime to provide the oxygen supply. These tiny arteries, which are hardly visible in CTA images and tend to be tortuous, are often impossible to detect in the previous levels.

Collateral and similar arteries have a diameter less than a couple of millimeters. In our algorithm, the maximum radius in this level is set to 1.5 mm whereas the minimum radius is limited by the voxel size. In the case of thin arteries, the partial volume effect may cause a loss of intensity. The algorithm, therefore, needs to adjust the blood intensity range for this level. The lower bound of blood vessel intensity range is lowered by 20% of the muscle intensity range [see Fig. 3(d)] and temporarily reset to $\theta_{low}^{b, \text{new}} = \theta_{low}^b - 0.2 * (\theta_{high}^m - \theta_{low}^m)$. The intensity value for the upper limit θ_{high}^b can stay the same as measured by the histogram analysis. Since these arteries have a very small radius, in many cases only 1 to 2 voxels, the inner, the outer, and the bounding ellipses are very small. The number of voxels on the perimeter of these ellipses is often insufficient for performing a proper filtering of the potential node voxels. Therefore, the detection step has to be modified. Potential node voxels are selected based on the blood vessel intensity range, but, in further examination by specialized filters, only filter nos. 4 and 5, which limit the minimum and the maximum radius, are used. In the node connection step, only connections shorter than `max_edge_length` are created. In this level, the value of `max_edge_length` is very short, only 10 mm, to reduce false artery detections.

An example of a volume is displayed in isosurface rendering mode with different intensity levels (see Fig. 3). Figure 3(b) shows a detailed cutout that the lower limit for the blood range—the threshold between blood and muscle tissue—which was automatically selected in histogram analysis, nicely separates bigger arteries from their surroundings. If we lower this intensity by shifting the threshold between blood and muscles by 10% of the muscle intensity range [Fig. 3(c)], we see that more parts of the tiny arteries were included within the blood intensity range. If we lower it even more by shifting the threshold so that 20% of the muscle intensity range now belongs to blood intensities [Fig. 3(d)], we detect even more of the tiny arteries. However, we also detect more noise scattered in the muscle tissue. For the node detection step, it is not advisable to lower the intensity beyond this limit since then we no longer see elliptical areas of blood intensities in the cross sections, but rather a very noisy mixture of blood and muscle intensities [Figs. 3(e), 3(f), and 3(g)] until a uniform plateau of intensities of the same range is reached.

Fig. 2 A 2-D axial slice of a volume. (a) Two cross sections of large arteries with severe calcification (enclosed by big red circles) and three cross sections of small arteries (enclosed by small green circles). (b) and (c) The same image with various threshold overlays marked with yellow color.

Fig. 3 A part of volume depicting bone and small arteries is displayed in isosurface rendering mode. (a) Broader view with marked region of interest and (b)–(f) shows cutouts with isosurface rendered with different intensity levels.

4 Evaluation and Results

The vascular skeleton extraction algorithm described in Sec. 3.2.4 was implemented in C++. In Sec. 4.1, this algorithm is demonstrated using real CTA data of the lower limbs and is validated against a reference and a united skeleton. For evaluation, two different metrics, an overlap rate M_o and a detection rate M_d , were applied.

4.1 Computed Tomography Angiography of the Lower Limbs

In our study, CTA data of the lower limbs were acquired from the clinical routine in patients with a suspicion of the lower limb PAD, where severe calcification and occlusions can be expected.¹⁸ We identified 28 consecutive cases to ensure that the characteristics of the sample agree with those of the relevant population.¹⁹ Three cases were excluded due to incomplete image data or amputations. The CTA scans from the abdominal aorta to the feet were obtained in the arterial phase using a Siemens Somatom Flash Scanner set to 80 kV and 228 mAs. The protocol included automated injection of 75 to 100 ml of iopromide (Ultravist) 370 mg J/ml at a rate of 3.7 to 4.0 ml/s, followed by 70 ml of isotonic saline injected at the same rate. The image volumes have an average size of $512 \times 512 \times 1711$ voxels with an average voxel size of $0.78 \times 0.78 \times 0.7$ mm³ and a bit depth of 16 bits.

4.2 Reference and United Skeleton

A “reference skeleton” and a “united skeleton” are both needed to properly evaluate our results. The reference skeleton was obtained from an experienced radiologist using an open source CTA analysis tool implemented as a plugin in Osirix software.²⁰ This is a semiautomatic tool, where the radiologist is required to mark several pairs of seed points—start and end seed points—and the software then computes the connectivity between given seeds. In healthy cases, a relatively low number of seed points are needed. However, in cases of severe calcification or where segments become occluded, the radiologist has to manually

track the segments. After the centerline is created, it needs to be manually inspected, and false centerline branches are cropped away. The whole process is time-consuming as it takes on average 20 min per case to create a reference skeleton. However, this skeleton was not complete as it is very tedious, if not impossible, to manually place seed points into every artery in the CTA scan. For this reason, validating our resulting skeleton only against the reference skeleton will not give a correct idea of the real performance of our algorithm. Thus, creating a united skeleton, computed as a union of our resulting skeleton and the reference skeleton was needed. A radiologist cleaned this united skeleton from spurious branches. The cleaning was done by removing centerlines detected inside the bones or beam hardening artifacts caused by metallic implants, so only a valid arterial skeleton remained. Using a segmentation algorithm proposed in Ref. 3, both the reference and the united skeletons were loaded in series into this level-set segmentation algorithm; thus, two 3-D arterial tree segmented models were generated. The 3-D models were visually checked for correctness. The 3-D model generated from the reference skeleton is named as the reference segmentation and the 3-D model from the united skeleton is named as the united segmentation.

4.3 Skeleton Evaluation Metrics

We use two evaluation metrics for validation, an overlap rate M_o and a detection rate M_d . When a skeleton A is compared to another skeleton B , the first metric M_o determines the portion of the skeleton A that is overlapped with the segmentation generated by skeleton B . The second metric M_d completes the information by giving the proportion of the skeleton B that was successfully detected by skeleton A .

In this section, we will explain what these two measures mean and how they are calculated on a concrete example when the detected skeleton from our proposed algorithm is compared to the reference skeleton. In this situation, the M_o measure returns the proportion of the detected skeleton that represents true artery centerlines. The M_d measure reveals how much of the overall true artery centerlines were detected by our algorithm. For evaluation purposes, the detected skeleton, as well

as the reference skeleton, has to be voxelized. A set of voxels created by the voxelization of the detected skeleton is denoted as N_d , and, similarly, N_r is a set of voxels from the voxelized reference skeleton. Moreover, S_r refers to the voxelized reference segmentation. By intersection of the N_d and the S_r sets, another subset C_d is created. This set contains voxels from voxelized detected centerlines that lie inside the voxelized reference segmentation. The detected skeleton is in general less centered; thus, it can contain fewer voxels than the reference skeleton within the same area, which may affect the results. Yet another two sets of voxels need to be introduced: $N_{d_centered}$ and $C_{d_centered}$. $N_{d_centered}$ contains voxels from the voxelization of centered detected skeleton, and $C_{d_centered}$ is defined as the intersection of $N_{d_centered}$ and S_r . The overlap rate M_o is then calculated as

$$M_o = \frac{|C_d|}{|N_d|} = \frac{|N_d \cap S_r|}{|N_d|}. \quad (1)$$

The detection rate M_d is determined as

$$M_d = \frac{|C_{d_centered}|}{|N_r|} = \frac{|N_{d_centered} \cap S_r|}{|N_r|}. \quad (2)$$

Note that M_o and M_d measures are the modification of more traditional precision and recall measures, respectively. However, since the proposed skeleton is approximate and is not overlapping the reference skeleton completely, measurements that allow a small displacement had to be used for evaluation.

4.4 Evaluation of Overall Performance

The two evaluation metrics M_o and M_d were calculated for all skeletons extracted by our algorithm from the 25 datasets. First, we evaluated the detected skeleton as compared to the reference skeleton. The average overlap rate $\bar{M}_o$ was 50%, and the average artery detection $\bar{M}_d$ was 75%. These numbers tell us that only half of what was detected by our skeleton was also detected by the radiologist, and, from what the radiologist had detected, three-quarters were covered by our detection. Visual inspection by an experienced radiologist concluded that most detected

Table 2 The overlap M_o and the detection rate M_d for three different comparisons. The results from Ref. 2 are shown together with the results of the newly proposed method. The reference skeleton is the same between the old and the new results, whereas the united skeleton differs between the two results.

Comparison	Old results from Ref. 2		New results from the proposed method	
	M_o (%)	M_d (%)	M_o (%)	M_d (%)
Detected skeleton to the reference skeleton	62.4	64.0	49.72	75.32
Detected skeleton to the united skeleton	97.4	71.3	89.12	82.13
Reference skeleton to the united skeleton	100	72.2	100	59.45

Bold values correspond to the result contribution of this paper.

Fig. 4 The overlap rate M_o and the detection rate M_d : (a) proposed method compared to the reference skeleton, (b) proposed method compared to the united skeleton, and (c) reference skeleton compared to the united skeleton, where M_o is 100% by mathematical necessity. The solid blue box extends from the lower to upper quartile values of the data, the solid red line marks the median value, and the solid black lines show the range of the data.

vessels were true vessels. As mentioned earlier, the comparison of the detected skeleton only to the reference skeleton would be misleading, since the reference skeleton does not contain centerlines of all the arteries in the human body. To get the true picture of the performance of the proposed method, the detected and the reference skeleton were evaluated against the united skeleton. For the proposed method, the average overlap rate $\bar{M}_o$ was 89% and the average artery detection rate $\bar{M}_d$ was 82%. For the reference skeleton, $\bar{M}_o$ was 100% and $\bar{M}_d$ was 59%. The mean values are reported in Table 2, and the median values with respective box plots are shown in Fig. 4.

4.5 Evaluation of Individual Level Performance

In this section, we present how each level contributes to the final result. The detected skeleton was cleaned by the radiologist from all spurious branches, as explained in Sec. 4.2, in the process of creating the united skeleton. Afterward, for each skeleton, the total length of true and false artery centerline segments, and the total number of true and false artery nodes detected were calculated. From the overall detected centerline length, 93% were true arteries and only 7% were centerlines detected in structures other than arteries. As for the number of nodes, 95% were true artery nodes and only 5% were nodes detected in other structures. The mean values are presented in the stacked bar plot on the left in Fig. 5. In addition, a statistics on how each level contributes to the total length of true and false artery centerline segments is presented in the form of box plots on the right side of Fig. 5.

4.6 Evaluation of the Running Time

Using an Intel Core i7-2760QM CPU@2.40 GHz and a C++ single-threaded implementation, the average running time of the proposed method was 196 s per CTA volume of mean matrix size $512 \times 512 \times 1711$ voxels. The first pass of the algorithm took an average time of 30 s, the second pass took an average time of 56 s, the third pass took 27 s, and the fourth pass took 83 s. An advantage of the proposed method is that detection of vascular nodes, as well as their connection, can be easily

Fig. 5 Statistics of the centerline segment length based on the classification into true and false artery categories and on the level in which the centerline connection was created. The box plots were contracted the same way as in Fig. 4. The circles indicate outliers.

parallelized. Using an OpenMP implementation on four CPU cores with two threads per core, the running time on the same test dataset dropped to an average of 70 s, thus giving a total parallel speedup factor of 2.8.

5 Discussion and Conclusion

The proposed cascading algorithm extends our previous work² and focuses on detecting the centerlines of arteries with severe calcification at one level and tiny arteries at another level. The

algorithm successfully improves the detection of tiny arteries in lower extremities as well as collateral arteries that create a bridge between two disconnected artery parts in the case of occlusion. Figure 6 shows an example from the clinical routine where occlusion is present in both the left and the right femoral artery and calcification occurs in the right iliac artery. Partial results after each of the algorithm levels clearly show that the connection through the calcified iliac artery was created at the third level. Similarly, at the fourth level, centerlines of many tiny

Fig. 6 An example of the results: (a) maximum intensity projection (MIP) of the volume. On the left side, MIP of three cutouts with manually removed bones is shown. The cutouts depict calcified iliac artery (top) and occluded femoral arteries (middle and bottom). (b) Partial results after each of the four levels (from left to right: first, second, third, and fourth level), (c) detected skeleton, (d) reference skeleton, (e) detected skeleton from the previous work.² In (b), the green (bright) color represents new true artery segments and the red (dark) color represents new false artery segments that were detected at each particular level. The black color represents segments detected at previous levels.

Fig. 7 A part of the volume depicting bones of a right foot displayed in isosurface rendering mode with intensity level equal to 600 HU overlaid with detected centerlines printed in red (dark) color.

arteries were detected. However, complete connection between two occluded parts of femoral arteries was not created. In this case, collateral arteries providing the blood supply to the distal body parts were smaller than the CT machine resolution and not detected by our algorithm as there was no intensity evidence strong enough to identify the connection. Even the experienced radiologist had to use additional knowledge about common anatomy and experience to be able to manually track some of the connections while preparing the reference skeleton for the evaluation. Therefore, not all our detected graphs are connected together.

The proposed algorithm was also able to detect, in some volumes, very distal artery branches in the foot, as shown in Fig. 7. Detecting these most distal arteries in the feet is clinically interesting, especially for the clinical question of vascular reconstruction. When considering whether to treat a stenosis in the tibial artery by open surgery or percutaneous angioplasty (balloon catheter), the presence of well-functioning arteries below the stenosis is of great importance. If the algorithm detects very distal arteries in the feet, this information increases the probability of a successful vascular reconstruction. However, many algorithms have problems detecting these most distal arteries.

The proposed method was validated against the reference and the united skeleton using the overlap rate M_o and the detection rate M_d . The same evaluation metric was used together with the same CTA dataset in our previous work.² Validation against the reference skeleton is directly comparable, since we used the same reference skeleton in both works. Whereas the detection rate M_d for the detected skeleton compared to the reference skeleton in Ref. 2 was 64%, the improved method reached 75%, meaning that a bigger part of the reference skeleton was detected in the proposed method. The same trend is visible when we compared the detection rate for the detected skeleton to the united skeleton. Old results show $M_d = 71\%$, and the new results show $M_d = 82\%$. For the overlap rate M_o , the portion of the detected skeleton overlapped with the reference skeleton, as well as the detected skeleton overlapped with the united skeleton, is smaller for the proposed algorithm than for the previous algorithm. This confirms the visual observation that the detected skeleton detects many centerlines that were omitted by the radiologist. The new method detects much more of the smaller and tinier arteries, which are also the ones easily missed by the radiologist. For the complete results comparison, see Table 2.

The quantitative performance of individual levels is analyzed in Fig. 5. The majority of the false artery segments were detected either within the surface of the bone or in the ray-like beam hardening artifacts caused by metallic implants. Both structures resemble an artery in terms of intensity and shape. In the case of the true artery segments, the second level contributes with the longest distance, while the first and fourth levels also improve

the results considerably. On the other hand, the third level, which specializes in detecting the centerlines of calcified arteries, contributes the least to the final result (2.5%). As for false artery detection, all levels erroneously detected similar amounts from overall centerline length (from the least error of 1.1% at the first level to the highest error of 2.6% at the second level). The third level contributes a comparable amount to the true as well as false artery centerlines. The reason is that by definition the third level detects centerlines of tubular structures that have wide range of intensities, including both blood and bone intensities. While the length of the arteries with severe stenosis forms only a fraction compared to the overall length of the centerline, it is very easy to detect longer portions of the bone once the centerline accidentally jumps from an artery to a nearby bone, since the bone intensities are included in the detection. These situations were rare; however, if they occurred, the incorrectly detected artery centerline inside the bone was relatively long. This caused the third level to bring almost the same amount of positive as negative benefits.

The proposed algorithm improves the centerline detection of arteries with severe calcification, tortuous collateral arteries, and tiny arteries in the lower extremities. The detection of distal artery branches in the feet has the potential to be used in the vascular reconstruction planning. A complete connection between two occluded arterial parts was, however, not always created as there was not sufficient intensity evidence to identify this connection. The main advantages of the proposed method are that it is fully automatic, it is possible to add new levels that can be adjusted to detect new vascular pathologies, and it is time efficient.

In future work, we would like to use a machine learning-based approach for the node detection step and let the classifier learn what the best features for distinguishing between the true and the false artery nodes are. Regarding the problem of detecting the incomplete connections between two occluded artery segments, a possible solution for the future would be to use the centerline tree results of our automatic method as a starting stage and let the radiologist deal only with the tasks that involve knowledge and experience. This combination would save a lot of time and effort by eliminating the need for placing the seed points to every artery manually. However, the method would not be fully automatic anymore. Although not tested in the present study, the approach described here could, in principle, also be applied to magnetic resonance angiography (MRA) data. Probably some modification of the algorithm would be needed, in view of the signal patterns of different tissues, which differ between CTA and MRA.

Disclosures

The authors have nothing to disclose.

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