Image processing in vascular computed tomography
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Citation for published version (APA):

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Evaluation of an improved technique for automated center lumen line definition in cardiovascular image data

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Eur Radiol. 2006 Feb;16(2):391-8

The original publication is available at http://www.springerlink.com http://dx.doi.org/10.1007/s00330-005-2854-2
ABSTRACT

The aim of the study was to evaluate a new method for automated definition of a center lumen line in vessels in cardiovascular image data. This method, called VAMPIRE, is based on improved detection of vessel-like structures. A multiobserver evaluation study was conducted involving 40 tracings in clinical CTA data of carotid arteries to compare VAMPIRE with an established technique. This comparison showed that VAMPIRE yields considerably more successful tracings and improved handling of stenosis, calcifications, multiple vessels, and nearby bone structures. We conclude that VAMPIRE is highly suitable for automated definition of center lumen lines in vessels in cardiovascular image data.

I. INTRODUCTION

Analysis of vasculature in patients suspected of atherosclerosis is of great importance as cardiovascular disease is one of the leading causes of death in the western world. Accurate and reproducible methods to analyze vessels, and most importantly the degree of stenosis, are crucial when considering therapeutical options. Traditionally Digital Subtraction Angiography (DSA) projection images have been the gold standard for stenosis grading. The shortcomings of visual assessment of these types of images have motivated the development of automated techniques to support vessel analysis, which resulted in programs such as Quantitative Coronary Angiography (QCA). Nowadays the required image data for diagnostic purposes on vessels is increasingly acquired using techniques such as Magnetic Resonance Angiography (MRA) and Computed Tomography Angiography (CTA), which are minimally invasive and yield three-dimensional (3D) image data. Part of the analysis of this image data is usually automated but nonetheless the observer is required to make (a considerable amount of) decisions which means that the whole procedure is still time consuming and highly user dependent. In the future these problems are expected to rise considerably given the continuing increase in the application of these non-invasive imaging techniques.
It is therefore crucial to develop automated methods for accurate, fast, robust and reproducible analysis of (atherosclerotic) vessels in CTA and MRA data. Automated analysis of vessels can be roughly divided into several steps: segmentation, quantification, and visualization. Segmentation is the basis for the other steps and typically involves definition of a center lumen line (CLL). This CLL can be defined manually (possibly supported by some form of automation) but the resulting CLLs have a high intra and inter observer variability.\textsuperscript{8-10} Automated definition of a CLL is called for and several methods have been published.\textsuperscript{1,11,12}

Aylward et al.\textsuperscript{13} grouped the path tracing methods into 3 approaches: explicit methods (directly targeting a CLL), implicit methods (whenever a CLL extraction is implied in methods to segment a tubular object), and post-processing methods (the lumen is segmented from which a CLL is calculated). Implicit and post-processing methods can be suitable techniques whenever a vessel tree needs to be extracted, e.g. for surgical planning and/ or guidance, or for centerline extraction for virtual colonoscopy.\textsuperscript{14} Unfortunately these methods appear less suitable for quantification of vessels.\textsuperscript{1,15} This is because automated segmentation of the lumen typically runs into problems in stenotic areas,\textsuperscript{16} especially in vessels with a small diameter such as coronary arteries. Here we focus on techniques for explicit path tracing as results from earlier studies and our own preliminary tests indicated that (some of) these techniques have the potential to cope with stenotic areas and may therefore be more suitable for the automated tracing of a CLL.

Over recent years a number of techniques for explicit automated path tracing in vessels have been published. The first approach is the use of iterative methods, i.e. a path grows in a search direction based on local properties.\textsuperscript{16} For example, Direct Vessel Tracking\textsuperscript{17} determines the middle of a vessel by performing a local search algorithm based on previously defined points and edge-detection of the vessel. Unfortunately, vessels of high curvature and vessels where the lumen area does not change gradually, such as in the transition to a stenosis or an aneurysm, cause considerable problems. In general, iterative methods fail in cases with severe stenosis or image degradation.\textsuperscript{16} A second approach centers on the use of filters specifically aimed at vessel-like structures.\textsuperscript{1,13,15-19} The results are very promising, but actual application in clinical procedures is hampered by the high computational cost.

The aforementioned techniques for explicit automated path tracing typically
run into problems when dealing with vessels with abnormalities such as stenoses, aneurysms, and calcifications, but also when dealing with bifurcations, vessels of high curvature and nearby other vessels and bone. These problems severely hamper application in clinical practice and only very few quantitative evaluation results have been reported so far. With this in mind we decided to implement and quantitatively evaluate a new method for automated definition of a CLL in cardiovascular image data based on improved detection of vessel-like structures. These technical improvements were first tested on 2D images of clinical data as a proof of concept. This paper briefly describes our method and presents the results of a multi-observer evaluation study performed on (clinical) cardiovascular image data.

II. MATERIALS AND METHODS

II.A. DESCRIPTION OF METHOD

Our method for automated CLL definition in cardiovascular image data is called ‘VAMPIRE’ (Vascular Analysis using Multiscale Paths Inferred from Ridges and Edges). The major progress in VAMPIRE comes from the combination of an improved ridge filter with standard Canny edge detection to enhance elongated structures. The ridge filter is based on a modified Hessian (second-order derivative matrix) and it has already been successfully applied for automated neurite tracing. We hypothesized that the modified Hessian, and corresponding ridge filter, should also be more sensitive to elongated structures such as vessels compared to vessel tracing techniques based on normal Hessian analysis (Fig. 1). In addition, Hessian analysis provides vector information (Fig. 2), which is highly suited to steer search algorithms in tracing a path. The actual implementation in VAMPIRE utilizes a multiscale version of the ridge filter, which makes it more suitable for the varying diameters of vessels in cardiovascular image data. The resulting edge and ridge information is used to calculate a cost image (Fig. 3). Subsequently, an implementation of Dijkstra’s shortest path algorithm based on the cost image and the vector information yields a minimal cost path.
Fig. 1
Visualization of the shapes of (a) the ridge filter based on normal Hessian analysis as described by Frangi et al., and (b) the ridge filter based on the modified Hessian as used in VAMPIRE. The use of the modified Hessian makes the corresponding filter more sensitive for vessel-like structures.

Fig. 2
The analysis of (a) the original image using the modified Hessian implemented in VAMPIRE yields vector information as shown as white lines for each pixel in the blow-ups of (b) and (c).

Fig. 3
(d) A cost image is calculated from (a) the original image based on (b) Canny edge filtering and (c) ridge filtering using the modified Hessian.
VAMPIRE is compared with a method based on a ridge filter for vessel enhancement using normal Hessian analysis,\textsuperscript{18} in combination with a minimal cost path algorithm (identical algorithm is used in VAMPIRE) as described by Wink et al.\textsuperscript{19} In short we will call this combination the Frangi-Wink method. Both the Frangi-Wink method and VAMPIRE were implemented as plug-ins in a public domain Java\textsuperscript{TM}\textsuperscript{23} image-processing program called ImageJ.\textsuperscript{24} The parameter settings were optimized for both methods and were fixed during the experiments. This strategy follows from earlier work by Sato et al.\textsuperscript{15} and our parameters were based on the same settings.

II.B. EVALUATION OF THE METHOD

In this evaluation study we used 21 slab maximum intensity projections (MIPs)\textsuperscript{25} with a thickness of 10 mms of multislice CTA image data from 14 patients with stenosis (>30\%) in the internal carotid artery (ICA). The slab MIPs were oriented in such a way that the common carotid artery (CCA), the ICA, and the external carotid artery (ECA) were visualized in one image. In these 21 slab MIPs a total of 40 tracings were obtained by focusing on the CCA plus bifurcation and either choosing the ICA (yielding 24 paths, as sometimes both ICAs were visible) or the ECA (yielding 16 paths) as secondary target.

Reference paths for each of the 40 tracings were obtained by manual path tracing performed by four qualified and trained observers. The datasets were blinded and given in different order to the observers. Each observer indicated points in the target vessel in each of the MIPs which were automatically connected by straight lines resulting in 160 CLLs (40 CLLs per observer). The path tracings were required to begin as proximal as possible in the CCA and track either the ICA or ECA as distal as possible. All paths, required time and required number of points were stored individually for each of the observers. Subsequently, a mean manual tracing was calculated from the paths of the four observers for each of the 40 vessels.

The automated tracings of Frangi-Wink and VAMPIRE were both initialized using the same start and end point. Whenever the defined path left the target vessel a live-wire\textsuperscript{26} implementation allowed placement of an additional point (performed by the main author, setting the total to three) to prevent the path from leaving the vessel. The minimal cost path algorithm in combination with the live-wire
implementation allows minimal observer-variability in the placement of the additional point within the target vessel, which implies that the resulting path is virtually observer-independent.

Evaluation of the tracings was based on calculating the deviation. This deviation was defined as the area spanned between a tracing and corresponding reference tracing divided by the length of the reference tracing (area/length). Consequently, the deviation for the manual tracings was determined by calculating the deviation for each observer using the mean tracing of the other three observers as reference. The deviation for an automated tracing (either the Frangi-Wink method or VAMPIRE) was assessed using the corresponding mean manual tracing as reference.

II.C. STATISTICAL ANALYSIS

The observer experiments were analyzed using a mixed model ANOVA. First we considered observer as fixed effect in order to test for systematic differences between observers; next we considered observer as random effect along with the vessels in order to estimate the between-vessel variance component and the two within-vessel components (between- and within-observer).

The paired Student t-test was found to be the most appropriate method for statistical analysis of the results of the automated methods. To obtain a normal (gaussian) distribution in the data the values were log-transformed. Significance is supposed to be reached for p-values below 0.05.

III. RESULTS

III.A. MANUAL TRACINGS

Table I shows results of the manual tracings for each observer using the average tracing of the other three observers as reference. Considering observer as fixed effect, the null hypothesis of equal manual tracing could be rejected (p = 0.028).
Pairwise comparison of the observers only revealed a significant difference between observers 1 and 3 ($p = 0.003; 95\% CI: 0.061 – 0.295$). When considering random effects, the total variance of the manual tracings equals 0.100 mm, of which 27\% is due to between-image variability. The remaining 73\% of within-image variability is the total of 4\% between-observer and 69\% within-observer variability. However, the between-image variability component of 27\% is an artifact caused by taking absolute deviations (spanned areas) of within-image measurements. This is because the definition of the tracing value of an observer is the absolute deviation from an average of absolute deviations from a reference tracing in the other three observers.

In-depth analysis of the manual tracings showed two situations, i.e., i) the observers produced virtually identical tracings in areas where the vessel could be considered normal, and ii) the observers produced considerable differences in abnormal areas, most notably in stenotic areas with calcifications (Fig. 5a).

### Table I
Path tracing results for the four observers

<table>
<thead>
<tr>
<th>Observer</th>
<th>Mean deviation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1</td>
<td>$1.08 \pm 0.33$</td>
</tr>
<tr>
<td>Observer 2</td>
<td>$1.02 \pm 0.29$</td>
</tr>
<tr>
<td>Observer 3</td>
<td>$0.90 \pm 0.29$</td>
</tr>
<tr>
<td>Observer 4</td>
<td>$0.99 \pm 0.33$</td>
</tr>
<tr>
<td>mean</td>
<td>$1.00 \pm 0.31$</td>
</tr>
</tbody>
</table>

* In mm with sd over all 40 path tracings for each of the four observers using the average of the other three observers as reference.

### III.B. USER INTERACTION

On average, the observers required $18.1 \pm 4.7$ points (including start and end point) and $41.9 \pm 14.0$ seconds for each of the manual vessel tracings. For the automated path definition the time needed to calculate the cost-image (essentially preprocessing) was 12 seconds on a Pentium IV 2 GHz. The subsequent definition of a minimal cost path (based on previously defined start and end points) was virtually instantaneous. Essentially the latter step was only limited by the required
user-interaction whenever the tracing left the target vessel. The time it took an observer to indicate all required points (i.e. start and end point and, when necessary, an additional point) in order to define a path using the automated methods was approximately 3 seconds per case. In short, the automated technique VAMPIRE considerably reduced the number of required clicks (from 18 to a maximum of 3) and required time (from 42 sec. to 3 sec.) per vessel in tracing atherosclerotic carotid arteries compared to manual vessel tracing.

**III.C. COMPARISON AUTOMATED METHODS**

The results of the path tracing based on a start and end initialization point using the automated methods Frangi-Wink and VAMPIRE were compared with the mean tracings of the four observers (see Table II). Statistical analysis revealed that the results for the automated methods Frangi-Wink and VAMPIRE were significantly different ($p = 0.000$, ci -1.710 - -0.910). Moreover, both methods yielded significantly different results when compared to the manual mean (Frangi-Wink: $p = 0.000$, ci = 1.646 – 2.503 and VAMPIRE: $p = 0.000$, ci 0.562 - 0.967), which is primarily caused by the automated tracings that left the target vessel. With the Frangi-Wink method 29 path tracings left the target vessel and with VAMPIRE this was limited to 7 cases.

| Table II |
| Results for the automated methods Frangi-Wink and VAMPIRE compared with the manual reference |
| Manual mean | Frangi-Wink† | VAMPIRE† |
| mean deviation* | 1.00 ± 0.31 | 16.33 ± 19.91 | 2.66 ± 2.32 |

*In mm. with sd. over all 40 path tracings.
†Both Frangi-Wink and VAMPIRE were initialized using the same start and end point.

These results show that, given the two initialization points, VAMPIRE clearly outperforms the Frangi-Wink method, but still requires improvements and/or more user interaction to produce acceptable tracings.
III.D. AUTOMATED METHODS: ADDITIONAL USER-INTERACTION

The benefit of additional user-interaction was assessed by adding one additional point whenever an automated tracing left the target vessel. Consequently, the results of the Frangi-Wink method and VAMPIRE were subdivided into three categories (Table III); (i) ‘2-point-success’: tracings initialized by one start and one end point that did not leave the target vessel; (ii) ‘3-point-success’: tracings requiring one additional point to stay in the target vessel; and (iii) ‘unsuccessful’: tracings leaving the target vessel even after an additional point is placed.

Without an additional point, there were 7 cases where VAMPIRE left the target vessel. This was caused by a nearby other vessel or overprojection of another vessel in the MIP (5 cases), or a nearby elongated calcification (1 case), or a combination of both (1 case). The results for these 7 cases with the Frangi-Wink method were worse compared to VAMPIRE, i.e. with the Frangi-Wink method 2 of these cases required an additional point and the remaining 5 cases were unsuccessful.

Given the additional point there were no cases where VAMPIRE tracings left the target vessel whereas the Frangi-Wink method still resulted in 20 tracings leaving the target vessel. Some of the tracings with the Frangi-Wink method needed up to 8 additional points to keep the tracing in the vessel.

Table III
Results for the automated methods Frangi-Wink and VAMPIRE after additional user-interaction.

<table>
<thead>
<tr>
<th>Category</th>
<th>Frangi-Wink</th>
<th>VAMPIRE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean deviation*</td>
<td>n†</td>
</tr>
<tr>
<td>2-point-success</td>
<td>1.58 ± 0.64</td>
<td>11</td>
</tr>
<tr>
<td>3-point-success</td>
<td>1.65 ± 0.91</td>
<td>9</td>
</tr>
<tr>
<td>Unsuccessful</td>
<td>7.06 ± 4.28</td>
<td>20</td>
</tr>
</tbody>
</table>

* In mm. with sd.
† n = number of cases.

The results for both automated methods for the categories 2-point-success and 3-point-success were statistically analyzed and compared to the manual mean. This test revealed that there was no significant difference between the automated methods Frangi-Wink and VAMPIRE with regards to the tracings in the categories.
2-point-success and 3-point-success (2-point-success: $p = 0.329$, $ci = -0.127 - 0.343$ and 3-point-success: $p = 0.908$, $ci = -1.961 - 1.917$). The mean values for both automated methods for the categories 2-point-success and 3-point-success were still significantly different from the manual mean (Frangi-Wink, 2-point-success: $p = 0.017$, $ci = 0.079 - 0.635$, VAMPIRE, 2-point-success: $p = 0.000$, $ci = 0.413 - 0.628$, Frangi-Wink, 3-point-success: $p = 0.009$, $ci = 0.140 - 0.720$ and VAMPIRE, 3-point-success: $p = 0.000$, $ci = 0.307 - 0.651$).

Several typical examples from the category ‘unsuccessful’ are depicted in Fig. 4. The paths defined using the Frangi-Wink method left the target vessel because of bone, calcifications, or another vessel, whereas the paths defined using VAMPIRE did not leave the target vessel. Characteristic examples of problems in defining a CLL in the current implementation of VAMPIRE are presented in Fig. 5b and Fig. 5c. Fig. 5b illustrates the problem of nearby or overlapping vessels in the MIP images and Fig. 5c illustrates swaying of the VAMPIRE path caused by calcifications and local variations of the edge of the lumen.
Fig. 5
Problems in defining a CLL: (a) observer tracings indicating differences in manual CLL definition especially in dealing with calcifications and bifurcations, (b) the proximity of another vessel causes the VAMPIRE tracing to leave the target vessel, and (c) paths defined using VAMPIRE occasionally exhibit swaying behavior.

IV. DISCUSSION

This study evaluates the combined effect of two technical improvements over earlier methods for explicit automated path tracing in clinical data, i.e., a filter more tuned to vessel-like structures and the combination with edge information. These technical improvements in VAMPIRE were first tested on 2D images of clinical data as a proof of concept. This setup not only saved considerable time and effort in implementing and testing the method, but also in the required manual labor for the path tracings by the clinicians. In addition, the 2D images made it very easy to visually assess the behavior of the automated (and observer) tracings.

VAMPIRE was compared with the method as described by Frangi and Wink and we found that the automated path definitions obtained with VAMPIRE were considerably more successful in tracing the target vessel with fewer problems in finding a CLL nearby stenoses, calcifications, multiple vessels and bone structures.
Given the design of the present study we cannot distill from the results whether and in what way this success can be attributed to the use of the modified Hessian or by the addition of edge information. This will be subject to further study. Moreover, Wink et al.\textsuperscript{16} recently published an improved version of the Frangi-Wink method. Their improvement is complementary to our improvements and will most probably be included in future versions of VAMPIRE.

The responses of the ridge filters for both the Frangi-Wink and VAMPIRE methods is dependent on the intensity, i.e. high intensities favor higher ridge responses. Originally the Frangi-Wink method was used for MRA image data where this intensity dependence can be regarded an advantage for vessel tracing. However, when applying these ridge filters on CTA data the intensity dependence implies that the traced path will be attracted to high HU values of calcifications and bone. This unwanted behavior was clearly noticeable with the Frangi-Wink method. The addition of the edge information in VAMPIRE seems to be a powerful mechanism to prevent the traced path to follow calcified structures. Another option to prevent the unwanted behavior could be to segment the calcified structures from the CTA data as a preprocessing step. Unfortunately, the HU distributions of the contrast in the vessel and the calcified structures typically overlap, which means that segmentation, e.g. by setting a single threshold, is not straightforward and may require (substantial) user input. More intricate segmentation methods for calcified structures in CTA such as proposed by van Straten et al. and Isgum et al.\textsuperscript{27-29} may be more appropriate. However, VAMPIRE tracings experienced little problems with the calcified structures and we therefore decided not to further pursue this.

Path definitions using VAMPIRE resulted in a slightly higher mean deviation in the 2-point-success tracings (1.71 mm) compared to Frangi-Wink (1.58 mm). Although this difference is not statistically significant we decided to analyze it more thoroughly. This difference appears to be caused by the swaying behavior (Fig. 5c) in the path definitions by VAMPIRE, which is probably due to two main factors. First factor is the sensitivity of the Canny edge filter to edges in the lumen caused by inhomogeneous contrast filling. This clearly caused the tracings to exhibit unwanted behavior when using VAMPIRE and a simple thresholding step of the edge information was implemented so as to suppress filter responses to small edges in the lumen. We anticipate that this threshold will no longer be necessary upon further optimizing the parameters for the calculation of the cost
image from the edge and ridge information. Second factor is the effect of small structures like calcifications and nearby bone structures, but also small variations in the edges of the vessel itself. The observers typically ignored these small effects, but it was not clear whether this was motivated by the aim to produce smooth paths or merely to save time and effort by taking shortcuts. This means that the question whether these small effects cause the VAMPIRE tracings to exhibit truly unwanted behavior can only be answered after standards have been developed for the definition of the CLL in clinical data.

Unique (mathematical) definition of a CLL in simulated and phantom data of vessels is possible, but unfortunately defining the CLL of a vessel in clinical cases is not trivial. The variation in the tracings performed by the observers made this very clear, especially in areas involving e.g. a bifurcation, stenosis, or calcification (see the tracings by each of the four observers in Fig. 5a). As a further complication different clinical questions may require different definitions of an ‘optimal’ path (not necessarily the CLL). For instance, the path for quantification of stenoses probably follows the center of the lumen whereas a path defined for stent placement may be required to follow the center of the vessel. As already implied earlier, standards have to be developed for the definition of the CLL in clinical cases.

The use of the minimal cost path algorithm to calculate the path implies that methods such as Frangi-Wink and VAMPIRE will tend to follow the inner curve of a vessel and not the center of the vessel. Whenever this behavior is unwanted it can be reduced or even prevented by using another algorithm to calculate a path in the cost image or by adding an extra processing step, e.g. using the local edge and/ or ridge information to optimize the location of all individual points of the tracing.

As already indicated earlier, Hessian analysis on multiple scales in 3D data is a problem because of the high computational cost. A local instead of global analysis of the Hessian can avoid this problem, e.g. by using thresholding-based pre-segmentation of the vessels. Other options are to perform the required calculations in a pre-processing step and/ or to use a parallel implementation on a multi-CPU machine using multi-threaded programming.

An important consequence of the obtained results is the fact that paths defined using VAMPIRE in the images we used are virtually independent of the observer. In 33 of 40 cases the required observer input in the MIP images of the carotid arteries was limited to the two initialization points. In the remaining 7 cases
one additional point was required. Additional software can be developed which takes these points as a first guess and investigates the neighboring edge and ridge information to locate optimal points (‘snapping’). This would effectively remove all observer-critical decisions in the definition of paths. The remaining observer input can even be replaced by using an atlas or (CLL) model (e.g. based on statistical analysis) in combination with nonlinear registration so as to provide the relevant initialization data. This would result in completely user-independent vessel tracing and the observer would only be required to verify the results of the path tracing.

The applicability of VAMPIRE was tested on image data from DSA, MRA and CTA in other clinical cardiovascular studies. Fig. 6 presents the results of VAMPIRE for a DSA image and MRA data, and in Fig. 7 a result for coronary CTA data is shown. No additional points other than a start and end point were required to yield these successful tracings. These promising results indicate the potential of VAMPIRE in other imaging modalities and/or other clinical cardiovascular applications.

![Fig. 6](image)

Examples of path definitions in aorta-iliac arteries using VAMPIRE in (a) a DSA image and (b) a MIP of an MRA dataset.
The result of our evaluation study indicate that automated vessel tracing in CTA images of the carotid artery with VAMPIRE is a robust technique which considerably reduces the amount of observer interaction and time compared to manual tracing. We conclude that the VAMPIRE approach is highly suitable for automated path definition in vessels in (clinical) cardiovascular image data. Further development of the technique is expected to yield fully automatic, observer independent paths (also in 3D) that may directly serve as CLLs in accordance with standards provided by clinicians.

V. ACKNOWLEDGMENTS

The authors would like to thank Marc de Kock and Berend Koudstaal for their assistance, and Dr. Paul Mulder for his guidance with the statistical analysis.
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