Author’s response to reviews

Title: Skeleton-based Cerebrovascular Quantitative Analysis

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Author’s response to reviews:

Responses to the Editor and Reviewers' Comments

Paper: Skeleton-based Cerebrovascular Quantitative Analysis

First we would like to express our sincere appreciation for the editor and all the reviewers for their valuable comments and suggestions. We have revised the paper, accordingly. The major issues addressing these comments are explained below and are presented in the revised version of our manuscript. Many thanks.

Reviewer #1:

General comments

The manuscript deals with an essential challenge to utilize quantitative methods to characterize the vasculature based on medical imaging. The methods are not revolutionary, but all of them have not obviously applied earlier to this purpose. The results are convincing. New tools are presented to perform quantitative analysis of curvature and torsion. Use of spheres to determine the vessel radii is also interesting. I do not see the end of the Introduction necessary.
Response: Thank you very much for your interest in our work. We agree with your suggestions and have deleted the final two sentences of the Introduction.

Detail comments

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1. The material is from an open source database. It should be described in the Methods and Materials section for the readers. The description should contain the health condition and age of the subjects, imaging modality (CT?, MR?, a), age of image data, use of contrast media, slice thickness and other imaging parameters. Without this information it is impossible to evaluate the applicability of the method.

Response: Thank you for your advice. We have rewritten the Method and Materials section. Specifically we have added a description of the health condition and age of the subjects, imaging modality used, date of image acquisition, the use of contrast media, slice thickness and other imaging parameters.

The new text is rewritten as follows:

This study included data from 108 3D TOF MRI sub-study participants with available good-quality head MRA. The data used were obtained from the open source database http://public.kitware.com/Wiki/TubeTK/Data in the MHA format[25]. The 108 sets of data were obtained from healthy population, with similar size and resolution. The data were not labeled with client or disease information. Data from subject number 47 were selected to illustrate the methodology used to calculate the different parameters and present the results with a size of 448×448 × 448 and resolution of 0.513393× 0.513393 × 0.800004 mm3. The No. 47 was a dataset pertaining to a 31-year-old female and her health status. The CoW from the patient was morphologically complete and unique applicable to each vessel of the CoW. The differences among the vessels are presented. The datasets supporting the conclusions of this article are included in the additional files. We have partially analyzed the 108 sets. For all datasets, denoising and regularity were the necessary pre-processing steps for subsequent study.

2. Remove: "The images come from the dataset, which is freely available as open data."

Response: We have deleted this sentence from the revised manuscript, as suggested.
3. The principles for calculating the curvature and torsion are well presented. However, the scales (minimum and maximum) should also be given for the reader, because they do not appear to have dimensions.

Responds: The curvature refers to a second-order differential and the torsion is the third-order differential. The scales of the curvature were \([0, +\infty)\) and the scale of the torsion were \((-\infty, +\infty)\), respectively. All these values are indicated in the manuscript.

4. The first chapter in Results (below) should be included in Methods and Materials:

This study included data from 108 MRI sub-study participants with available good-quality head MRA data. The data were not labelled with client or disease information. Data from No. 47 were selected to illustrate the calculation methodology of the parameters and present results. The datasets supporting the conclusions of this article are included within the article's additional files.

Responds: Thank you for your advice. We agree with your advice and have shifted illustration of the data into the Methods and Materials. The paragraph has been rewritten as suggested.

5. Please explain the code "Data from No. 47". I assume that this an image set of a "typical case". The authors should give basis to the choice.

Responds: No. 47 is the image number of an image dataset. We have now described the rationale behind this decision as follows:

“The No. 47 was a dataset pertaining to a 31-year-old female and her health status. The CoW from the patient was morphologically complete and unique applicable to each vessel of the CoW. The differences among the vessels are presented. The datasets supporting the conclusions of this article are included in the additional files. We have partially analyzed the 108 sets. For all datasets, de-noising and regularity were the necessary pre-processing steps for subsequent study.”

6. In Discussion you should describe the problems and challenges encountered when analyzing some other image sets.

Responds: Thank you very much for this important suggestion. We decided to use geometric methodology for population analysis. Partial studies have been conducted with the new image set. In last part of the discussion, we described the problems and challenges of these studies as follows.
The paragraph is rewritten as follows:

“In spite of the promise of this new method, it is also associated with some problems and challenges. For example, the resolution and the image sequences may vary significantly in different datasets. In addition, the estimation parameters and fitting error for the segmentation method and B-spline fitting method may be altered based on a new dataset. The automated topology recognition needs to be further optimized. Nevertheless, we believe that the robust nature of the L1 method means that good results can be obtained on a large dataset. It should be noted that the current study only addresses the geometric factors in one example data set. Consistency with physician judgment should be verified in a double blind study. These results should also be extended to a larger experimental analysis. Accordingly, future studies will investigate open source data and Chinese large-population data.”

7. Page 10, row 16: "Usually, the physician and radiologist prefer to evaluate the cerebrovascular volume value via shape analysis". Please state whether you mean visual inspection or manual measurement.

Responds: We mean that physicians and radiologists prefer to use visual inspections for shape analysis. More studies have investigated topology rather than geometry.

We have rewritten the sentence as follows:

“Under normal circumstances, physicians and radiologists prefer to evaluate the cerebrovascular volume using shape analysis. The topological structure is always analyzed by visual inspection, which yields rough quantitative data.”

8. First to chapters of Discussion: Please indicate your sources as references.

Responds: The first paragraph in the Discussion highlight the importance of geometric analysis of the cerebral artery. This paragraph has been rewritten and four important papers have been cited. This new paragraph is as follows:

The quantification and analysis of cerebral artery geometry, particularly the arteries that constitute the CoW, is of great interest[1]. Pathological changes in the cerebral arteries mainly appear in three patterns:

1) lumen stenosis of the cerebral arteries due to atherosclerosis[2],
2) DE and tortuosity caused by injury to the intima or elastic tissue injury in the tunica media vasorum[3], and

3) vascular stiffness due to loss of elastic fibres in the vascular wall[4].


9. Page 14, rows 10 to 27: Indicate the authors of the references, for instance "Bullit et al [34].
Response: We have checked all the references in the paper, and have cite them in the correct format. Thank you for bringing this to our attention.

10. Page 16, row 57: The calculation takes 10 minutes? Do you mean the whole process, mainly the time used by the operator?
Response: Our method and pipeline are automated. The time taken to obtain this single data set was less than 10 minutes, including all the operators. The automated calculations of skeleton and topology accounted for most of the time. The sentence has been rewritten on page 15 as follows:

“The calculation of this single dataset lasted less than 10 min as all operations. The automated calculations for the skeleton and topology accounted for most of this time. The current algorithm and pipeline indicate the fundamental efficiency of large population-based calculation and analysis.”

11. In Discussion please also estimate the robustness of the method. How sensitive it is to the data? Would it work for a typical clinical MRI or CT study?
Response: In our methodology, the pipeline is robust to the clinical MRI data. The segmentation method is a statistics method with PSO used to estimate the parameters. The robust nature of the method was shown in our previous study (reference 25 in the manuscript).


The skeletonization of the pipeline was based on L1 method to calculate the skeleton and topology. This method is very robust for the L1 character in neighbor distance calculation. We have completed the study and writing of the manuscript. A few images are shown in Fig. 1, partly supporting the robust methodology. The theoretical analysis and large-scale analysis of the experiments prove will be reported in an upcoming manuscript.

Fig. 1. Robust L1 methodology.
(a) The segmentation volume data of the CoW
(b) The addition of 10% Gaussian noise to the original data
(c) The addition of 20% Gaussian noise to the original data
(d)-(f) Use of the template method to obtain the skeleton from (a)-(c)
(g)-(i) Use of the L1 method to obtain the skeleton from (a)-(c)

12. I recommend removing the last sentence in Discussion: "Some early works have been conducted using some of these data, and the results should be reported shortly."

Response: We have deleted this sentence from the Discussion

13. Reference Nr. 28 is incomplete

Response: We have verified the references and have now completed #28.

14. Figure 4: explain the coding of the colors of the lines

Response: We have explained the coding of the colors in the lines indicated in Figure 4.
15. Table 1: Is this the data for all subjects/image sets of the data? How many subjects?
Response: Table 1 includes data from only data No. 47. All the data from the whole image set will be reported in the future.

16. All tables: The calculated values shall be given by the accuracy of the method and data. For instance, the initial image does not have a micrometer resolution, you cannot give the results with three decimals. I recommend that you remove at least the last digit from all results.
Response: Thank you for this suggestion. We have removed the last digit from all the results. I have read the head data of the image: 0.513393 * 0.513393 * 0.800004 (mm*mm*mm). We have rewritten the data resolution description in the Methods and Materials section with three decimals. The average values of the arc length of the branch were within (0.007, 0.163)mm and the variation of the errors were within (0.00005, 0.043)mm. We cannot explain data with two decimals clearly.

17. Figure 7 / Caption: Here you should shortly describe what kind of data you have: imaging modality, slice thickness etc.
Response: We have rewritten the description of the data in the caption for Figure 7, as suggested.

18. A language revision is needed. There are several expressions to correct, such as: de-nosing Geometric modelling extraction Here as we are interested in CoW.
Response: The English usage errors mentioned in your comments have been checked, and the language in the entire paper has been checked by a native English speaker.

Reviewer #2:
General comments
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Nice work although poorly suitable for clinical use, to date (as you wrote).
Response: Thanks a lot for your interest in our work. In a future study, we will report data with potential clinical application.
A physician can use this methodology as a useful tool to explain population research. Further, clients can use the data as follows:

“Currently, neurologists and radiologists not only focus on the cerebral artery stenosis, but also are interested in delineating the geometric characteristics of the arteries, such as elongation, dilation and tortuosity. Previous studies[34, 35, 36, 37] correlated dilatative arteriopathy with cerebral vascular disease. Identifying these factors was mainly based on reading manual images and vessel diameter measurements, with different scale. However, the consistency, accuracy, and ed. Stability, accuracy, and efficiency all need to be analyzed in subsequent studies. In the current study, we developed a skeleton-based automated segmentation algorithm using a TOF MRA dataset, which provided different geometric parameters to evaluate the vascular structure including radius, length, curvature, torsion, and the included angle. This method could be applied to other cerebral arteries, such as the basilar artery or internal carotid artery, to investigate the association between artery geometric structure of arteries and cerebral vascular disease.”

Detail comments

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1. You did not mention the average age of your healthy patients; maybe you referred to fully-developed patients (>18 YO). A table could probably fit to this purpose as well as few lines regarding the developing vessels in developing brains...

Response: This study included data from 108 3D TOF MRI sub-study participants with available good-quality head MRA. The data used were obtained from the open source database http://public.kitware.com/Wiki/TubeTK/Data in the MHA format [25]. The 108 sets of data were obtained from healthy population, with similar size and resolution. The data were not labeled with client or disease information. Data from subject number 47 were selected to illustrate the methodology used to calculate the different parameters and present the results with a size of 448×448 × 448 and resolution of 0.513393 × 0.513393 × 0.800004 mm3. The No. 47 was a dataset pertaining to a 31-year-old female and her health status. The CoW from the patient was morphologically complete and unique applicable to each vessel of the CoW. The differences among the vessels are presented. The datasets supporting the conclusions of this article are included in the additional files. We have partially analyzed the 108 sets. For all datasets, denoising and regularity were the necessary pre-processing steps for subsequent study.

2. -I did not understand how you and your method could manage anatomical variants and/or embryological remnants (i.e. persistent Trigeminal artery, persistent Hypoglossal artery and so on...).
Response: Thank you for raising this important point. Anatomical variants and/or embryological remnants occur frequently in the CoW in the population. We used the machine learning method to label the anatomical variants and/or embryological remnants with the Maximum a posteriori estimation (MAP). This work is another important study being performed by our laboratory; we have finished the work and are currently writing up the work.

3. I did not understand how and what you could develop as a "suitable tool" for clinical imaging technique and/or calculation of normality; maybe a CT/MR software?

Response: We have developed a software with the methodology. The software is coded with C++ and VTK 5.0. This software has been partly used in the Peking Union Medical College Hospital to perform 2D medical images, virtual endoscopes of the brain vessel, 3D visualization of the brain and skeleton and skeleton calculations of the CoW.

4. Compliments for your job.

Response: Thank you very much for your kind words and encouragement. We will work hard to perform more interesting and meaningful work in the future.

Reviewer #3:

General comments

This is a study describing an automated shape analysis method for characterising the geometry of the Circle of Willis (CoW) using automated segmentation and shape approximation via B-spline skeletonisation. While the motivation for developing a robust, automated method to quantify CoW geometry is well (yet too exhaustively) explained, the paper lacks structuring and clarification of the applied methodology and consequently presents inconclusive results. The concluding statement that the example data "verified the stability" of the method is unclear and is not supported by the data.

Response: Thank you very much for your advice and suggestions. We have reconstructed the paper and clarified the methodology used. The purpose of this manuscript was to present the methodology pipeline. Data analysis involving large populations will be presented later. We used the B-spline to fit the discrete points of the skeleton. In the “verified stability” part of the study, we aimed to demonstrate that the fitted results were consistent with the original data points. In a
later explanation, (in the additional files) we use the state-of-the-art results provided by the client physicians to confirm the accuracy.

Detail comments

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1. The abstract omits the methods section, which makes it more difficult to grasp the purpose of the study. The actual methods section, however, is full of equations referring to known relations such as arc length, curvature or torsion, which have been described previously and which do not represent a novel contribution. In fact, large parts of the work seem to rely on known frameworks such as ITK/VTK or VMTK (The Vascular Modeling Toolkit [1]). This is not an issue in itself, however, the shape analysis pipeline is sold as a novel methodology, without clearly stating the authors' original contributions. Centreline computation and vessel radius and curvature derivation, for instance, can be easily obtained via VMTK.

Response: Thank you for your suggestion. We have rewritten the abstract to include the research aim in the background. We have also added a method section to illustrate the pipeline of our method.

Response: We agree that methods to calculate the arc length, curvature, or torsion of the continuous model are widely used in geometric analyses. The main contribution of the paper is as follows. First, we integrated all these methods to design an automated pipeline for the 3D geometric quantification of the CoW. The segmentation and the skeletonization methods were designed by us. Second, to determine the discrete skeleton point of the vessel, we used a B-spline curve for a stable quantification.

Response: We agree that VMTK can enables determination of the centerline of the corresponding vessel. But manual selection of the source and target points is essential, which has insufficient automation and is subject to human error. The current method is fully automated and eliminates human error. We performed experiments using the same data with VMTK and our method. The results and illustrations are shown below:

The right panel shows the results obtained using VMTK and the left panel shows the data obtained with the current method. With little deviation of the point selection in VMTK, the result will be changed substantially.

Even with comparatively accurate starting point and end point selection, the big bend in the vessel, the skeleton obtained with our method is much better than that of the VMTK shown in the red and yellow circles. In the small branch of the vessel the skeleton is always missing with VMTK, shown as green circle. The bright part in the radii of the branch was calculated using the VMTK under visualization; which is also not very accurate. These limitations associated with
VMTK prompted us to undertake this study. We apologize that this was not illustrated clearly in the pre manuscript.

2. Very confusing indeed is the fact that until the last paragraph of the Discussion, the Reader does not know how many subjects were actually studied. The authors introduce earlier the open source TubeTK database comprising 108 subjects. Then, one subject (No. 47) is used to describe the analysis pipeline in detail (which is fine). Yet, the Results section is full of geometric data, leaving the Reviewer unsure whether the full 108 subjects were studied - until the Discussion section reveals that all data was obtained from subject No. 47.

Response: We are very sorry that you were confused about the data source. In fact, only single source of data was used to illustrate the pipeline of our methodology. In the abstract, materials and results, we emphasized that the study involved only one subjects No.47. In the future, we will analysis additional data using the methodology and report interesting geometric relationships between the branches of CoW.

3. The question remains what to do with all that data. The average and variance (one would typically expect the standard deviation or standard error instead of the variance) of radii, curvatures and lengths of certain sections of the CoW do not tell the Reader anything of relevance regarding the "stability" or goodness of the used methods. Furthermore, the Reviewer is left unsure about the meaning of the included significance tests, i.e. p-values. What was the null hypothesis? What exactly was compared or analysed?

Response: Thank you for your suggestion. The data illustrate the feasibility of the methodology. The data is consistent with the client knowledge. The stability of the methodology was confirmed using a double-blind validation with a client physician. Please see our response to point 5 below for a more detailed explanation. We have checked the significance tests, as suggested.

4. The most severe problem of this paper is that it lacks comparison versus an acknowledged gold standard. The authors refer to "stability" or "confirmation" of the methods. What really should be investigated though, are validity (i.e. accuracy) and/or reliability (i.e. repeatability) of the methodology. This should already start at the point of segmenting the CoW from medical image data. This certainly being a difficult task, one could imagine a separate study presenting segmentation results of an automated segmentation algorithm compared to a reference segmentation (which presumably would be manual segmentation/labelling
performed by experts). Validity should here be assessed by computing Dice scores, for example.

Response: Thank you very much for this advice. We agree that the stability and confirmation of the method should be verified. The segmentation methodology stated in the manuscript was reported in a prior study. The validity and reliability of the method have been established in our previous study (reference #25 in the manuscript, as shown below). The consistency of the method and comparison with manual segmentation results is illustrated and the Dice score is provided. Therefore, in this study, we did not emphasize its significance.


5. Furthermore, results from an automated geometric vessel characterisation should be compared against reference values, which again most likely would be manual measurements taken by (clinical) experts. Ideally, such studies should involve more than one subject and could make use of the TubeTK database, as it is readily available. Once actual validity of the proposed methods has been demonstrated and properly quantified, one could finally think about a study presenting geometric CoW data of a clinically interesting cohort, and - as the Authors suggest - try to establish associations between geometric features and clinical outcome.

Response: Thank you for raising this important point. As suggested we performed a double-blind validation by the client physician. The physician uses the Osirix to calculate the radii of each branch. Manual measurement enables calculation of only two radii of the branch. Without the process registration, the two points do not represent the same arc length sample point from the branch, suggesting the limitation associated with manual calculation. However, the data are consistent with our results..

The first table shows the radii calculated by our method. The first line is the number of the example point; the units is mm. The second table was calculated manually based on the initial MRA data by the physician with Osirix. The unit is also mm. Apparently, the manual measurements are all showed in the max and min results.
Radius calculated by our methodology. (mm)

Example

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Radius calculated by the doctor. (mm)

Example

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<tr>
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<td>1.20</td>
<td>1.43</td>
<td>1.77</td>
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</tr>
</tbody>
</table>

6. The current study however, does not prove the accuracy of the proposed framework nor does it provide clinically relevant insight and is thus not suitable for publication in BMC Medical Imaging.

References
I do not feel that the accuracy and/or consistency of the proposed methods have been adequately quantified and demonstrated in this paper. Instead, trivial equations and geometric data of one generic subject is presented, without providing any technical or clinical insight.

Response: Thank you for your advice. Some of our work, such as segmentation, skeletonization, and quantity analysis, have been used to serve clients in the Peking Union Medical College Hospital. In the revised version of the manuscript, we will focus and emphasize the accuracy and consistency of the proposed method.

Response: As suggested, we have revised the manuscript with clinical insight. Some of the paragraph has been rewritten as follows:

“Neurologists and radiologists presently not only focus on cerebral artery stenosis, but also are interested in geometric characteristics of the arteries such as elongation, dilation, and tortuosity. This is because previous studies revealed an association between dilatative arteriopathy and cerebral vascular disease. Identifying these latter factors relies mainly on reading manual images and vessel diameter measurements, with a different level of scale evaluation. However, the consistency, accuracy, and efficiency of this method cannot be verified. Stability, accuracy, and efficiency all need to be analyzed in subsequent studies. In the current study, we developed a skeleton-based automatic segmentation algorithm from a TOF MRA dataset, which provided different geometric parameters to evaluate vascular structure including radius, length, curvature, torsion, and the included angle. This method could be applied to other cerebral arteries, such as the basilar artery or internal carotid artery, to explore the association between artery geometric structure and cerebral vascular disease.”


