Peer Review File

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Reviewer A

1. It would be valuable to explicitly state how the findings of this study are relevant to clinical practice and patient outcomes, a clearer connection between the research and its potential impact on healthcare is needed.

Reply 1: We really appreciate your comment. In the "Introduction" section of the manuscript, we introduced the important role and potential impact of this study in medical health. For example, we have expressed in the article that coronary artery segmentation is an important step in a series of tasks in clinical trials, such as plaque assessment, stenosis detection, and centerlines extraction. The method we have developed can accurately segment coronary arteries, reduce the burden on doctors to read CT slices, and help achieve an automatic and objective system for detecting coronary artery stenosis and plaques.

Changes in the text: "Introduction" section, page 2, lines 3-11, page 3, lines 1-10.

2. The author must include a separate section for Strengths, Weaknesses, and Extensions of the current research.

Reply 2: Thank you for your suggestion. We have added a subsection titled "Strengths, limitations and future works" in the discussion section, which explores the advantages and disadvantages of our method and its expansion in future work. Please refer to the revised copy of the manuscript we submitted for specific modifications.

Changes in the text: "Discussion" section, "Strengths, limitations and future works" subsection, page 15, lines 14-35, page 16, lines 1-7.

3. Benchmarking Table of current research against the previous study should be provided by the author.

Reply 3: Thank you for your comments. We have modified the Benchmarking Table labeled "Table 1" in the text. The results of comparing our method with four other benchmark methods are presented in this table. The CV method and Jawaid et al.'s method are our implementations in this dataset, while the UNet and VNet methods were obtained from the study of Qiu Y et al.(44) conducted in the same dataset. Meanwhile, we have revised the description of quantitative analysis in the text to better illustrate the performance of our method and we have added references to the research involved in the added method as follows:

42. Ronneberger O, Fischer P, Brox T. U-net: Convolutional networks for biomedical image segmentation. Medical image computing and computer-assisted intervention–

MICCAI 2015:18th international conference, Munich, Germany, October 5-9, proceedings, part III 18. Springer International Publishing 2015;234-241.
43. Milletari F, Navab N, Ahmadi S A. V-net: Fully convolutional neural networks for volumetric medical image segmentation.2016 fourth international conference on 3D vision (3DV). Ieee 2016;565-571.
44. Qiu Y, Chai S, Zhu E, et al. Deep multi-scale dilated convolution network for coronary artery segmentation. BIOMED SIGNAL PROCES 2024;92:106021.
Changes in the text: "Results" section, page 12, lines 28-32, page 13, lines 1-2.

4. The paper should delve deeper into the clinical relevance and potential applications of the local region active contour model approach in CAD diagnosis. A discussion of bias in CAD systems and potential mitigation strategies would enhance the analysis. Explore potential sources of bias and their impact on clinical decision-making.
Reply 4: We agree with your suggestion. Our method may encounter biases in application, and we have added in the article the possible scenarios of biases and their impact on clinical decision-making. Finally, we have provided corresponding mitigation measures to ensure the good performance of the method. In short, our method was only validated on a public dataset with a small sample size, so our method may not be robust enough in application. The reason for the bias may be mainly due to the different image quality of different CT machines and the individual differences in the medical examination performed by clinicians on patients. In order to mitigate the bias, we believe that a good anti-bias effect can be achieved by adjusting the pre-process steps in the method. Please refer to the revised copy of the manuscript we submitted for specific modifications.
Changes in the text: "Discussion" section, page 14, lines 34-36, page 15, lines 1-12.

Reviewer B

This is a technical report on 3D coronary artery segmentation based on local region active contour model. Most of the content of the paper is the development of the algorithm. I suggest the authors to revise the paper to make it understandable by medical professionals. In the discussion, the authors should have comments on the limitations of the developed algorithm in this study and suggest future research directions. It is also important to discuss the potential clinical implications of the current findings.

Reply: We really appreciate your thoughtful comment. We have revised the content in the article to make it more closely related to medical health, making it easier for medical professionals to understand the meaning of the article. Specifically, we elaborated on

the weaknesses of our method in the "Strengths, limitations and future works" subsection and discussed the current clinical implications of our findings at the beginning and end of the article. Please refer to the revised copy of the manuscript we submitted for specific modifications.

Changes in the text: "Introduction" section, page 2, lines 3-11, page 3, lines 1-10;

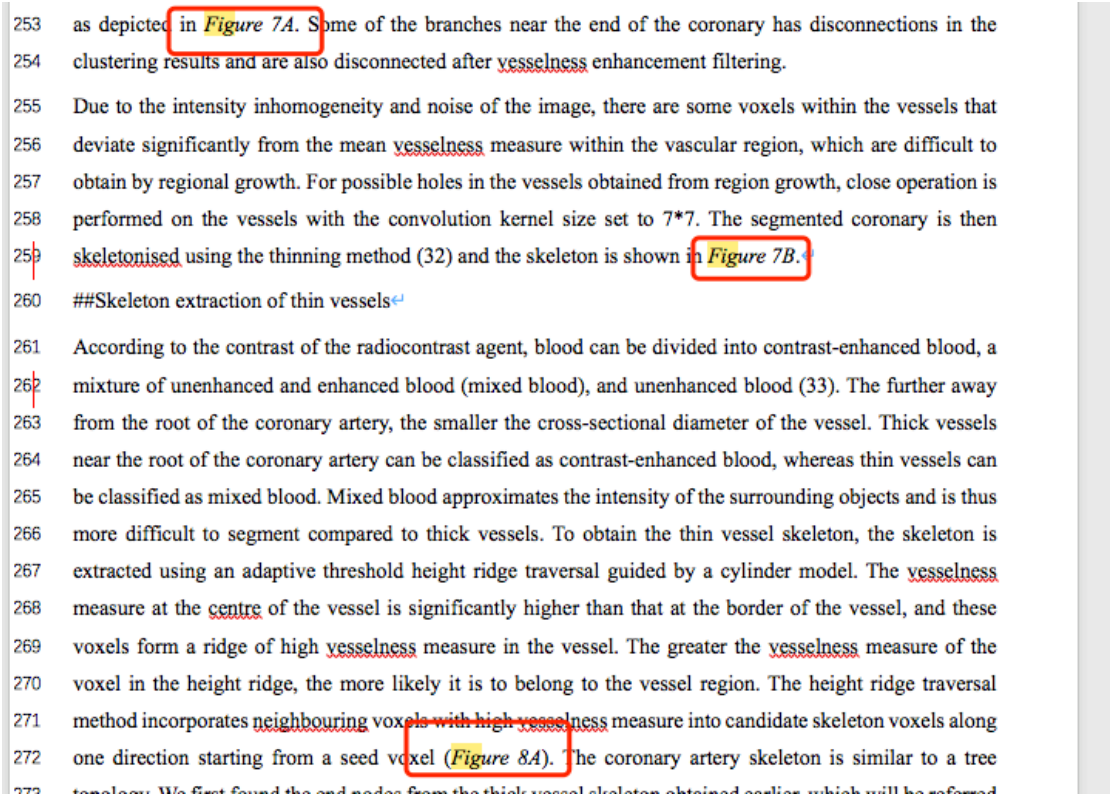
"Strengths, limitations and future works" subsection, page 15, lines 14-35, page 16, lines 1-7;

"Conclusions" section, page 16, lines 31-32.

Reviewer C

1. **Figure 7C should be cited consecutively between figure 7B and figure 8A. Please revise.**

Figures should be cited consecutively in the text and numbered in the order in which they are discussed. *(example: Figure 1 contains 4 parts, such as Figure 1A, 1B, 1C, 1D, these parts should also be cited consecutively, unless Figure 1 is already cited before Figure 1A, 1B, 1C, 1D.)*



253 as depicted in *Figure 7A*. Some of the branches near the end of the coronary has disconnections in the
254 clustering results and are also disconnected after vesselness enhancement filtering.
255 Due to the intensity inhomogeneity and noise of the image, there are some voxels within the vessels that
256 deviate significantly from the mean vesselness measure within the vascular region, which are difficult to
257 obtain by regional growth. For possible holes in the vessels obtained from region growth, close operation is
258 performed on the vessels with the convolution kernel size set to 7*7. The segmented coronary is then
259 skeletonised using the thinning method (32) and the skeleton is shown in *Figure 7B*.
260 ##Skeleton extraction of thin vessels
261 According to the contrast of the radiocontrast agent, blood can be divided into contrast-enhanced blood, a
262 mixture of unenhanced and enhanced blood (mixed blood), and unenhanced blood (33). The further away
263 from the root of the coronary artery, the smaller the cross-sectional diameter of the vessel. Thick vessels
264 near the root of the coronary artery can be classified as contrast-enhanced blood, whereas thin vessels can
265 be classified as mixed blood. Mixed blood approximates the intensity of the surrounding objects and is thus
266 more difficult to segment compared to thick vessels. To obtain the thin vessel skeleton, the skeleton is
267 extracted using an adaptive threshold height ridge traversal guided by a cylinder model. The vesselness
268 measure at the centre of the vessel is significantly higher than that at the border of the vessel, and these
269 voxels form a ridge of high vesselness measure in the vessel. The greater the vesselness measure of the
270 voxel in the height ridge, the more likely it is to belong to the vessel region. The height ridge traversal
271 method incorporates neighbouring voxels with high vesselness measure into candidate skeleton voxels along
272 one direction starting from a seed voxel (*Figure 8A*). The coronary artery skeleton is similar to a tree

359 we could obtain fast convergence of the LSF. *Figure 7C* shows the results of the final segmentation using
360 the active contour model. We found that the proposed method can efficiently segment almost all thick vessels

Reply: In order to meet the order requirements of image citation, we have modified the images as follows: We merged A and B from the original Figure 7 with the original Figure 8 into one image (**Figure 7**), and merged C from the original Figure 7 with the original Figure 9 into one image (**Figure 8**). Therefore, the original Figure 7 has been

discarded, and at the same time, the original Figure 10 has become **Figure 9** and the original Figure 11 has become **Figure 10**. **Now we only have ten images in our manuscript.** We also modified the **figure legend** corresponding to the image at the same time.

After making the above modifications to the images, we found that Figure 8C is slightly blurry compared to Figures 8A and Figures 8B, so we replaced it with a clearer version.

Changes in the text: We highlighted the citations of Figures 7 to 10 in yellow in the manuscript.

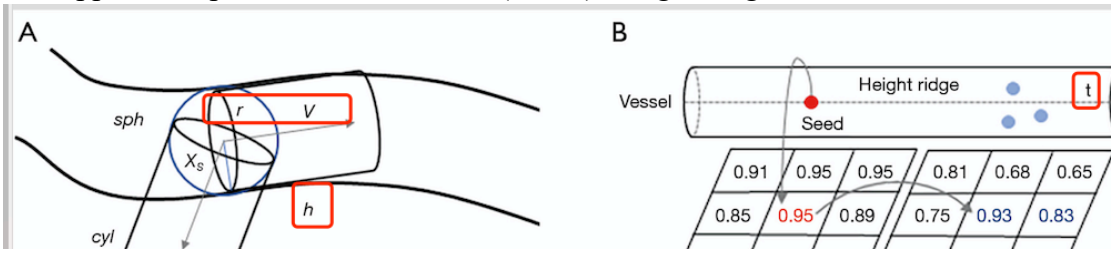
"Methods" section, line 277, line 292, line 317, line 320, line 325, line 328, line 364;

"Results" section,line 376, line 412, line 416, line 419, line 425.

The figure lengend of Figures 7 to 10, lines 705-727.

2. Figure 8

a. If applicable, please the full term of (r, V, h) in figure legend.



Reply: We have added the meanings of these abbreviations in the figure legend.

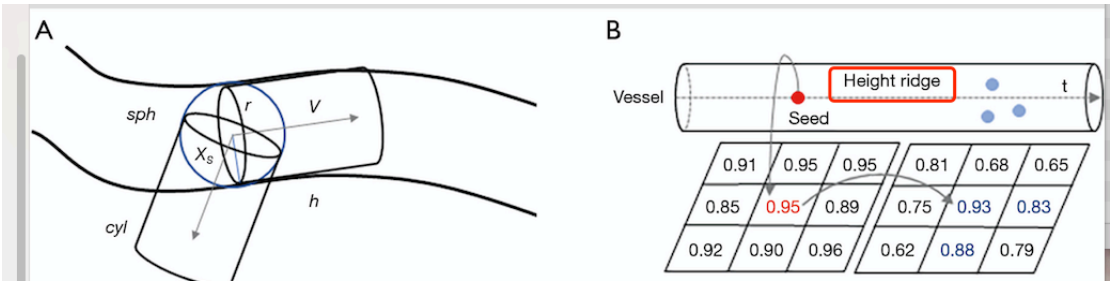
Changes in the text: The figure lengend of figure 7, lines 708-709.

b. It seems that the citation of figure 8A match figure (B); the citation of figure 8B match figure (A). Please also check the figure legend, and revise.

voxel in the height ridge, the more likely it is to belong to the vessel region. The height ridge traversal method incorporates neighbouring voxels with high vesselness measure into candidate skeleton voxels along one direction starting from a seed voxel (*Figure 8A*). The coronary artery skeleton is similar to a tree topology. We first found the end nodes from the thick vessel skeleton obtained earlier, which will be referred

guide the extraction of candidate skeletons, which is inspired by (18). The cylinder model is shown in *Figure 8B*, and the details are explained as follows:

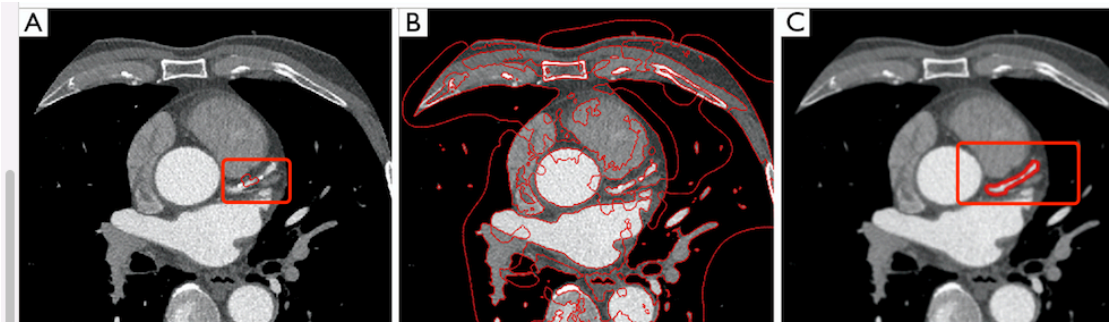
Figure 8 Schematic diagram of cylindrical model and height ridge traversal. (A) Schematic diagram of the cylindrical model. (B) Schematic diagram of height ridge traversal. (shp represents the sphere and cyl represents the cylinder.)



Reply: Thank you for your reminder. We adjusted their order in Figure 7.
Changes in the text: The figure lengend of figure 7, lines 708-709.

3. Figure 9

Please explain the red line area in figure legend, if necessary.



Reply: Thank you for your suggestion. We have added the following statement to the legend : "the area enclosed by the red curve represents the segmentation result obtained "
Changes in the text: The figure lengend of figure 8, lines 711-712.

4. Table 1

How were these data presented in your Table? mean±SD? mean±SEM? Please either give explanations inside Table or in table footnote.

Table 1 The segmentation performance of the five methods, measured by precision, recall and DSC.

Methods	Precision	Recall	DSC
Jawaid et al. (41)	0.8022±0.0607	0.8290±0.0941	0.7408±0.0698
CV (38)	0.7765±0.0552	0.7286±0.1039	0.6832±0.1064
UNet (42)	0.748 ± 0.08	0.837 ± 0.10	0.787 ± 0.06
VNet (43)	0.759 ± 0.06	0.849 ± 0.08	0.806 ± 0.08
Our method	0.8664±0.0734	0.9126±0.0720	0.7913±0.0815

CV, Chan-Vese active contour model. DSC, dice similarity coefficient.

Reply: Thank you for your suggestion. We have added the following statement at the table footnote: The indicator value is expressed in the form of "mean+SD".
Changes in the text: Table 1 footnote, lines 683-684.

5. Please check the accuracy of this sentence.

and DSC of this method are 86.64%, 91.26%, and 79.13%, respectively. Our method has the highest precision and recall, while DSC is on par with VNet while surpassing the other three methods. Considering

Reply: Thank you for your suggestion. We have revised the expression of that sentence as follows: "Our method scored the highest in precision and recall, and was on par with the VNnet method in DSC. "
Changes in the text: "Results" section, lines 402-403.