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2D and 3D Vascular Structures Enhancement Via Improved Vesselness Filter and Vessel Enhancing Diffusion

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ABSTRACT In medical imaging practice, vascular enhancement filtering has been widely performed before vessel segmentation and centerline detection, which provides important pathological information and holds great significance for vessel quantification. In the literature, numerous well known vesselness filtering approaches have been developed. For example, some techniques explore the Hessian matrix of the original images and construct the vessel filter based on the eigenvalues of the Hessian matrix. In this work we develop a hybrid technique for fast and accurate vascular enhancement filter, which contains two main steps: vesselness diffusion and improved vesselness filter based on the eigenvalues ratio. This novel approach is quantitatively and qualitatively tested on the public 2D retinal datasets and 3D synthetic vascular structure models. Experimental results demonstrate that the proposed filter outperforms other existing approaches for curvilinear structure enhancement from noisy images. Moreover, the novel approach is further evaluated on real patient Coronary Computed Tomography Angiography (CCTA) datasets with ground truth regions labelled by professional cardiologist. Our method is proven to produce more accurate coronary artery segmentation results. Given the accuracy and efficiency, the proposed vesselness filter can be further used in medical practice for vascular structures enhancement before vessel segmentation and quantification.

INDEX TERMS Vascular structures detection, improved enhancement filter, Hessian matrix, vesselness diffusion, vessel segmentation.

I. INTRODUCTION

Vascular structures detection plays an utmost role in various applications of medical image processing and analysis, for example, cardiovascular disease screening [1], [2]. In clinical practice, automatic vessel segmentation methods usually achieve poor performances on CT scans due to the plaques and surrounding structures, and low intensity difference between coronary structures and surrounding tissues. In modern medical imaging, many approaches are developed for medical images denoising, e.g., X-ray cardiovascular angiogram images. For example, in [3] a novel smooth and convex surrogate function is first proposed as a replacement of the prior nuclear norm. Then, the proposed surrogate function is approximated by its first order Taylor expansion. Finally, a novel model called iterative weighted nuclear norm minimization scheme is proposed. In [4] the authors propose a novel iterative weighted sparse representation (IWSR) scheme for X-ray cardiovascular angiogram image denoising. First, a maximum a posterior (MAP) distribution by the Bayes' theory is adopted to simultaneously estimate the image and its sparse representation. Second, the MAP problem is converted to minimise an energy function using the logarithmic transformation. Third, the function is efficiently solved by the single and effective alternating directions method. In [5] the authors have proposed a spatially adaptive image denoising (SAID) method for X-ray angiogram images denoising, which contains two steps: spatially adaptive gradient descent (SAGD) image denoising and dual-domain filter (DDF).

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Vessel enhancement techniques have been widely used as a common prerequisite in biomedical imaging [6]–[10] before vessel segmentation and centerline detection, which holds great significance for coronary artery stenosis quantification. Normally, this enhancement phase can be conducted during the image pre-processing procedure by data acquisition and image analysis techniques. In the present context, large numbers of vascular structure enhancement approaches have been proposed [11]–[15]. Truc *et al.* [16] review three main categories of methods: linear filters [17], non-linear filters [18], [19] and Hessian-based multiscale filters [6], [13], [14], [20], [21]. Linear filtering methods often filter images by using Gaussian kernels or Gabor filters. However, they may filter vessel edges as well as thin vessel branches, which make them inappropriate to complex structures. Non-linear anisotropic diffusion filters can take place in certain structure direction since they use the information of the structure tensor orientation. Hence, they are able to preserve important features during the filtering process. Therefore, non-linear filtering methods are commonly used in medical imaging tasks. For example, in [19] the author combines the eigensystem analysis with a non-linear anisotropic diffusion scheme, in which the direction and the amount of the diffusion rely on the local vesselness response at each voxel location. However, diffusion based methods are not capable of detecting vessels within a wide range of scales, since they act at a fixed size.

Another way to identify vascular structures is to enhance tubular structures by using Hessian-based methods [6], [13], [14], [20], [21]. For example, in [20] the authors propose a novel enhancement filter based on ratio of multiscale Hessian eigenvalues. These kind of methods utilize the eigensystem of the Hessian matrix of image intensities to detect tubular structures. The main advantage of such a method is that it can be performed in a multiscale manner to detect objects of different sizes. More specifically, The Hessian matrix is calculated by exploring the second-order Gaussian derivatives at multiply scales, which is controlled by standard deviation. However, the Hessian matrix is only used for local geometric features of the image. As the vascular structure is enhanced, other tubular structures such as soft tissues are also enhanced during this process. As a result, some pseudo blood vessels and a large number of isolated noise points are enhanced, which increases the difficulty of coronary arteries segmentation. In addition, tensors have a principle limitation that they cannot simulate a complex image structure with only a symmetrical sphere.

Recently, diffusion tensors, like the Fractional Anisotropic Tensor (FAT), have been widely used to advance the detection of vascular structures [22]. FAT normally measures the variance of anisotropy across different shapes of vessels, which enables that FAT can better detect junctions and return more uniform vessel responds. Thus, FAT has great potential in medical images processing, like diffusion tensor regularization. For example, the method in [23] explores the feasibility of detecting vascular structures based on the Hessian matrix. However, the method introduces too many parameters and threshold values, which makes it difficult to be used for other medical datasets.

In modern medical imaging, manual extraction and annotation of vascular regions is time-consuming and skill-demanding. On the other hand, the performances of the existing vascular enhancing approaches vary easily due to artifacts and surrounding noises. Furthermore, it is a grand challenge to identify the vascular directions at junctions. As a result, accurate and automatic vessel enhancement approaches with minimal user interaction are in great demand. We are committed to improving the quality of medical images by filtering noises and enhancing edges, and using the smoothness suitable for the underlying image structure to maintain edges. A three-dimensional nonlinear anisotropic diffusion filtering method is introduced. The diffusion tensor proposed in this work is controlled by the image structure tensor. As a result, the main diffusion takes place along the vessel direction of the underlying image. A novel diffusion tensor, which is based on and extended from Frangi's vesselness measure, is developed to control the vesselness enhancement diffusion for CT images. Besides, the theoretical supports of the enhanced Frangi's vesselness measure and the diffusion tensor are mainly described. The superiority of the proposed 3D improved vesselness filter based on the ratio of eigenvalues is also studied in this paper.

The main contributions of this work are summarized in the following aspects: 1) A detailed review of related work about vascular structures enhancement in medical images is presented. 2) The enhanced Frangi's vesselness measure is proposed by multiplying an exponential term, which ensures that it is smooth at the origin and can be substituted into the diffusion equation. The theoretical support is also presented. 3) The manuscript includes detailed studies of diffusion tensor construction for anisotropic diffusion equation. 4) A detailed theoretical support of the new improved vesselness filter is given. Figure 1 depicts the flowchart of the proposed vesselness enhancement filter. First, original medical images are processed as input. Second, the Hessian matrix of each voxel in the 3D data is computed, and the enhanced Frangi's vesselness measure is calculated. Next, vesselness enhancement diffusion is performed for original medical images. The enhanced Frangi's vesselness measure is used to construct the diffusion coefficient. Finally, the Hessian matrix is again computed. Given the new eigenvalues, the proposed vessel enhancing filter can be designed.

The proposed vesselness filter is described in Section 2, which includes two main parts: 1) Frangi's filter based vesselness enhancement diffusion. 2) improved enhancement function based on the eigenvalues ratio of the Hessian matrix. Section 3 presents the experimental results on public 2D retinal datasets, 3D synthetic vascular structure models and 3D real patient Coronary Computed Tomography Angiography (CCTA) datasets. In Section 4 we give a brief discussion about the proposed enhancement approach. Finally, conclusions are given in Section 5.

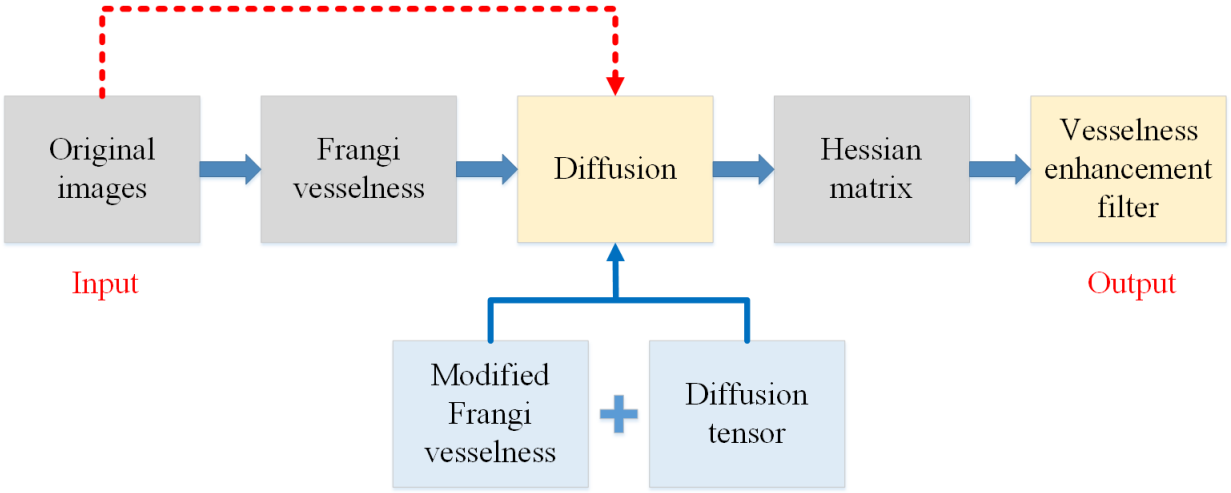

FIGURE 1. The flowchart of the proposed vesselness enhancement filter.

II. METHODOLOGIES

A. VESSELNESS ENHANCEMENT DIFFUSION

Medical images can first be pre-processed by utilizing vessel enhancing techniques [24]. The divergence form of the diffusion equation is commonly given by:

$$\frac{\partial L}{\partial t} = \nabla \cdot (D \nabla L) \tag{1}$$

where $L(x, y, z)$ is the original image, t the diffusion time and D the diffusion tensor. The diffusion tensor D usually is defined as:

$$D = \begin{bmatrix} D_{11} & D_{12} & D_{13} \\ D_{21} & D_{22} & D_{23} \\ D_{31} & D_{32} & D_{33} \end{bmatrix} \quad with \quad D_{ij} = \sum_{n=1\ldots3} \lambda_n v_{ni} v_{nj} \tag{2}$$

where v_1, v_2, v_3 with $v_1 = [v_{11}, v_{12}, v_{13}]$ are the eigenvectors of the structure tensor. In Weickert's work [25] the eigenvalues are computed by a from 2D to 3D extended equation. In the literature, there are mainly two possibilities for the extension from 2D to 3D. The first type is edge enhancing diffusion (EED) whose diagonal elements are defined as:

$$\lambda_1 = 1 \tag{3}$$

$$\lambda_2 = 1 \tag{4}$$

$$\lambda_3 = 1 - \exp\left(\frac{-3.31488}{(GMS/\lambda_e^2)^4}\right) \tag{5}$$

where $GMS = ||\nabla_\theta L||^2$ represents the gradient magnitude square, and λ_e planar structure contrast parameter. In this way, diffusion along the edge direction still takes place, but diffusion perpendicular to an edge is inhibited. Another type is coherence enhancing diffusion (CED) [19] whose diagonal elements are defined as follows:

$$\lambda_1 = \alpha - (1 - \alpha) \exp\left(-\frac{C}{k}\right) \tag{6}$$

$$\lambda_2 = \alpha \tag{7}$$

$$\lambda_3 = \alpha \tag{8}$$

with α is the global smoothing constant which is between 0 and 1, C is the edge enhancing smoothing constant and k is a parameter. The amount of smoothing is determined by the number of iterations set by the user.

In this work, Frangi's vesselness measure needs to be modified and used to construct the new diffusion tensor. Frangi's vesselness filter is defined as:

$$\mathcal{V}_F(\vec{\lambda}) = \begin{cases} 0 & \text{if } \lambda_2 > 0 \text{ or } \lambda_3 > 0 \\ (1 - e^{-\frac{A^2}{2\alpha^2}}) \cdot e^{-\frac{B^2}{2\beta^2}} \cdot (1 - e^{-\frac{S^2}{2\gamma^2}}) & \text{otherwise} \end{cases} \tag{9}$$

where $|\lambda_1| \leq |\lambda_2| \leq |\lambda_3|$ are the eigenvalues, and α, β and γ are weighting parameters. A, B and S are initially introduced to represent different vascular structures and given by:

$$A = \frac{|\lambda_2|}{|\lambda_3|} \tag{10}$$

$$B = \frac{|\lambda_1|}{\sqrt{|\lambda_2 \lambda_3|}} \tag{11}$$

$$S = \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2} \tag{12}$$

In the literature, the multiscale vesselness function $\mathcal{V}_F$ is used to construct the diffusion tensor based on the Hessian matrix eigensystem. The purpose of this paper is to design a diffusion tensor D for vascular enhancement, which makes it possible to use multiscale methods for vessel analysis. Unfortunately, the $\mathcal{V}_F$ defined in (9) cannot be used directly in (1) because of its non-smoothness at the origin. Therefore, an enhanced vesselness function $\mathcal{V}_s$ is developed [26]:

$$\mathcal{V}_s(\sigma) = \begin{cases} 0 & \text{if } \lambda_2 \geq 0 \text{ or } \lambda_3 \geq 0 \\ e^{-\left(\frac{2c^2}{|\lambda_2|\lambda_3^2}\right)} & \\ (1 - e^{-\frac{A^2}{2\alpha^2}}) \cdot e^{-\frac{B^2}{2\beta^2}} \cdot (1 - e^{-\frac{S^2}{2\gamma^2}}) & \text{otherwise} \end{cases} \tag{13}$$

where $e^{-\left(\frac{2c^2}{|\lambda_2|\lambda_3^2}\right)}$ is the novel term developed to multiply by the original $\mathcal{V}_F$ with a constant parameter c. The parameter c is used to result in a smoothed version of the vesselness function. The term $e^{-\left(\frac{2c^2}{|\lambda_2|\lambda_3^2}\right)}$ resembles a Gaussian function with its argument inverted, and it is controlled by the standard deviation c. In order to only have influence around the origin, the constant c should be chosen very small. There are two reasons for multiply the term $e^{-\left(\frac{2c^2}{|\lambda_2|\lambda_3^2}\right)}$. First, this term satisfies the differential property, approaches one near the origin and is one elsewhere. Second, after multiply the term, the enhanced Frangi's measure can be used to construct the diffusion coefficient and numerically substituted into the diffusion equation. For ideal tubular structures, the diffusion process guarantees that the diffusion strength is maximal and hence thin vessels can be preserved. For non-vessel structures, the diffusion strength is isotropic and high and noises can be removed. The maximum vesselness response is selected to perform the multiscale approach:

$$\mathcal{V} = \max_{\sigma_{min} \le \sigma \le \sigma_{max}} \mathcal{V}_s(\sigma) \tag{14}$$

The novel diffusion tensor D that incorporates the new vesselness measure $\mathcal{V}$ and is defined as: [18], [19]:

$$D \triangleq Q\Lambda' Q^T \tag{15}$$

where Q is the eigenvectors of the Hessian, and the diagonal matrix Λ' contains the following diagonal entries:

$$\lambda_1' \triangleq 1 + (\omega - 1) \cdot \mathcal{V}^{\frac{1}{S}} \tag{16}$$

$$\lambda_2' = \lambda_3' \triangleq 1 + (\epsilon - 1) \cdot \mathcal{V}^{\frac{1}{S}} \tag{17}$$

with parameters $\omega > \epsilon$, $\epsilon > 0$ and $S \in \mathbb{R}^+$. ω is the parameter controlling the diffusion strength ($\omega > 1$). Small positive value is chosen for ϵ. For ideal tubular structures, $\mathcal{V} \to 1$, the parameter ω works on λ_1' and guarantees that the diffusion strength is maximal. For non-vessel structures, $\mathcal{V} \to 0$, the parameter ϵ works on both λ_2' and λ_3' and allows that the diffusion strength is isotropic and high.

B. IMPROVED VESSEL FILTER

Once original medical images are pre-processed by utilizing the proposed vessel enhancing technique, the Hessian matrix at each voxel location is again computed, and the eigensystem is explored. The purpose of this section is to design an vesselness filter function in the form of the ratio of eigenvalues. The filter is not proportional to any eigenvalue and, at the same time, is robust to low-magnitudes of the eigenvalues. Compared with vesselness filters of other forms, this type of vesselness filter has two main advantages. First, it returns a response is close-to-uniform. Second, it enables that the response is invariant to object contrast. These two advantages play an utmost role in balanced and accurate vesselness enhancement [22], [27].

One example of the ratios of eigenvalues is called the volume ratio, which is used to detect nearly-spherical tensors and defined as:

$$V_{volume} = \lambda_1\lambda_2\lambda_3 \left(\frac{3}{\lambda_1 + \lambda_2 + \lambda_3}\right)^3 \tag{18}$$

It can be shown that the value of V_{volume} is in the range [0, 1]. To detect both elongated and spherical structures V_{volume} can be modified by substituting λ_1, with $\lambda_3 - \lambda_1$, which results in:

$$V_{mod} = (\lambda_3 - \lambda_1)\lambda_2\lambda_3 \left(\frac{3}{2\lambda_3 - \lambda_1 + \lambda_2}\right)^3 \tag{19}$$

However, such a vesselness filter may be ill-defined at low values of $|\lambda_2|$ and $|\lambda_3|$, and is sensitive to image noises in regions with uniform intensities. The value of λ_3 is therefore regularized at each scale σ as:

$$\lambda_{reg} = \begin{cases} \lambda_3 & \text{if } \lambda_3 < \tau \min_x \lambda_3(x, \sigma) \\ \tau \min_x \lambda_3(x, \sigma) & \text{otherwise} \end{cases} \tag{20}$$

where $\tau \in [0, 1]$ is a cut-off threshold parameter. High value of τ represents larger difference between $|\lambda_2|$ and $|\lambda_3|$ for low contrast structures. Otherwise, it indicates smaller difference between $|\lambda_2|$ and $|\lambda_3|$. Here λ_3 is regularized using function *min*() since we process images with bright structures on dark background (all the eigenvalues negative). Moreover, the value of $|\lambda_1|$ is relatively small, compared with $|\lambda_2|$ and $|\lambda_3|$. Thus it can be omitted, and $|\lambda_3|$ is replaced by λ_{reg} in (19), which yields the vesselness function:

$$V'_{mod} = \lambda_2\lambda_{reg}^2 \left(\frac{3}{\lambda_2 + 2\lambda_{reg}}\right)^3 \tag{21}$$

Furthermore, to explore vascular structures with elliptic cross-sections, we have the following relations:

$$\lambda_2 \approx \lambda_3 \; and \; \lambda_2 \ge \lambda_3 \tag{22}$$

note that both λ_2 and λ_3 are negative.

Without loss of generality, we consider the ratio $\frac{\lambda_2}{\lambda_3}$ in the range [0.5, 1], for vascular structures with elliptic cross-sections, which corresponds to the relation:

$$\lambda_2 \le \lambda_3/2 \tag{23}$$

since both λ_2 and λ_3 are negative. Recall that λ_3 is regularized, we have

$$\lambda_2 \le \lambda_{reg}/2 \tag{24}$$

which requires that the vesselness function (21) equals to 1 when $\lambda_2 \le \lambda_{reg}/2$. Therefore, it is achieved by substituting λ_{reg} with $\lambda_{reg} - \lambda_2$ in (21) and fixing the value to 1 for

$\lambda_2 \geq \lambda_{reg}/2$. Finally, the proposed vesselness function is given by:

$$\mathcal{V} = \begin{cases} 0 & \text{if } \lambda_2 > 0 \text{ and } \lambda_3 > 0 \\ \lambda_2(\lambda_{reg} - \lambda_2)^2 \left(\dfrac{3}{2\lambda_{reg} - \lambda_2} \right)^3 & \text{if } \lambda_2 \leq \dfrac{\lambda_{reg}}{2} \\ 1 & \text{otherwise} \end{cases} \tag{25}$$

The proposed vesselness function is designed based on the ratio of eigenvalues, which can return nearly uniform intensity profile for tubular structures. It is straightforward that when the value of τ decreases, the value of λ_{reg} will increase. As a result, it is more likely that $\lambda_2 > \lambda_{reg}/2$, which makes $\mathcal{V}$ to be 1. The idea behind the vesselness function is that it gives a more uniform response on bright structures for $\tau < 1$. Moreover, the proposed vesselness function returns a uniform response for varying contrast of raw image intensities, due to the eigenvalue ratio defined in (25). Therefore, the proposed vesselness function is capable of producing high and highly uniform response for vascular structures of interest with varying contrast of intensities.

III. RESULTS

In this section, the proposed method is both quantitatively and qualitatively evaluated against three different categories of datasets: public 2D retinal dataset, 3D synthetic vascular models and 3D real patient CCTA datasets. The accuracy of the new method is compared with that of the state-of-the-art approaches. The Receiver Operating Characteristic (ROC) curve is used to perform the visual comparison. Also, the Area Under the Curve (AUC) of the ROC curve is explored as the evaluation metric to compare the performances between the proposed vessel enhancing filter and the state-of-the-art techniques. Our hybrid vesselness filter for vascular structures enhancement takes the advantages of vesselness enhancement diffusion, and integrates the improved Frangi's filter based on the ratio of eigenvalues of the Hessian matrix. The proposed method is mainly compared with Frangi's filter [14], Jerman's method [20] and multiscale fractional anisotropy tensor (MFAT) method [23]. The main reasons are summarized in the following aspects: 1) Frangi's filter is widely used, since it is easy to implement, and returns very high response uniformity on objects with uniform intensities. In our work, we have first modified the original Frangi's vesselness filter by multiplying an exponential term to make it smooth at the origin. Then it can be used in the diffusion equation. 2) Jerman's method represents the category of enhancement filters that are based on the ratio of multiscale Hessian eigenvalues, and it achieves the state-of-the-art performance for this category of enhancement filters. 3) The MFAT method represents the category of non-linear anisotropic diffusion filters that use the information of the structure tensor orientation, and it achieves the state-of-the-art performance for this category of vessel filters. The proposed vascular enhancing method is implemented on a 16 GB of RAM Windows laptop. The parameters in the diffusion part are chosen as: total diffusion time 15s and time step 0.25s, $c_1 = 10^{-3}$, $c_2 = 10^{-5}$, $\rho = 2$, $\sigma = 1$. The eigenvalues used in this part are given by VED type.

TABLE 1. A comparison of mean AUC values between the state-of-the-art methods and the proposed approach over the DRIVE and STARE retinal datasets.

Approaches	AUC value	
	DRIVE	STARE
Frangi [14]	0.888	0.898
Jerman [20]	0.909	0.927
MFAT [23]	0.940	0.950
Proposed	**0.954**	**0.962**

A. 2D RETINAL IMAGES

To explore the effectiveness and accuracy of the proposed vascular structure enhancement approach, two publicly available retinal image datasets: DRIVE [28] and STARE [29], are used to present a more rigorous form of quantitative validation. Particularly, the proposed approach is evaluated against the state-of-the-art techniques. First, a visual inspection of the mean ROC curve, that represents some qualitative information, can be conducted. In addition, quantitative information, i.e., the mean of AUC between the ground truth vessels and the filtered results, are also presented.

Figure 2 presents the detected retinal vascular structures by using different enhancement methods, compared with the specialist labelled ground truth vessel structures. It can be observed that Jerman's method can extract only main branches, a lot of thin vessel branches are missing. Besides, large region of artifacts is introduced in the high intensity area (Figure 2(d)). In Figure 2(e), the MFAT method is able to return more thin vessel branches, and remove the large region of artifacts. However, many thin branches are isolated from the main branches. The proposed method is shown to detect most vessel branches, thin vessels are connected to the main branches, and no artifact is introduced by our approach. Figure 3 demonstrates a comparison of the intermediate retinal vascular results of the proposed vesselness enhancement method. The hybrid strategy is shown to give more complete and accurate retinal vessel structures.

Furthermore, the mean AUC values between the ground truth vessels and the filtered results by Frangi's filter, Jerman's method, MFAT method and the proposed method, are also presented in Table 1. Generally, higher values of AUC represent better vascular structure enhancement results. If the enhancement result is found to be identical to the ground truth, it will return the AUC value of 1. Given the qualitative and quantitative results, the proposed vessel enhancing method slightly outperforms the state-of-the-art methods.

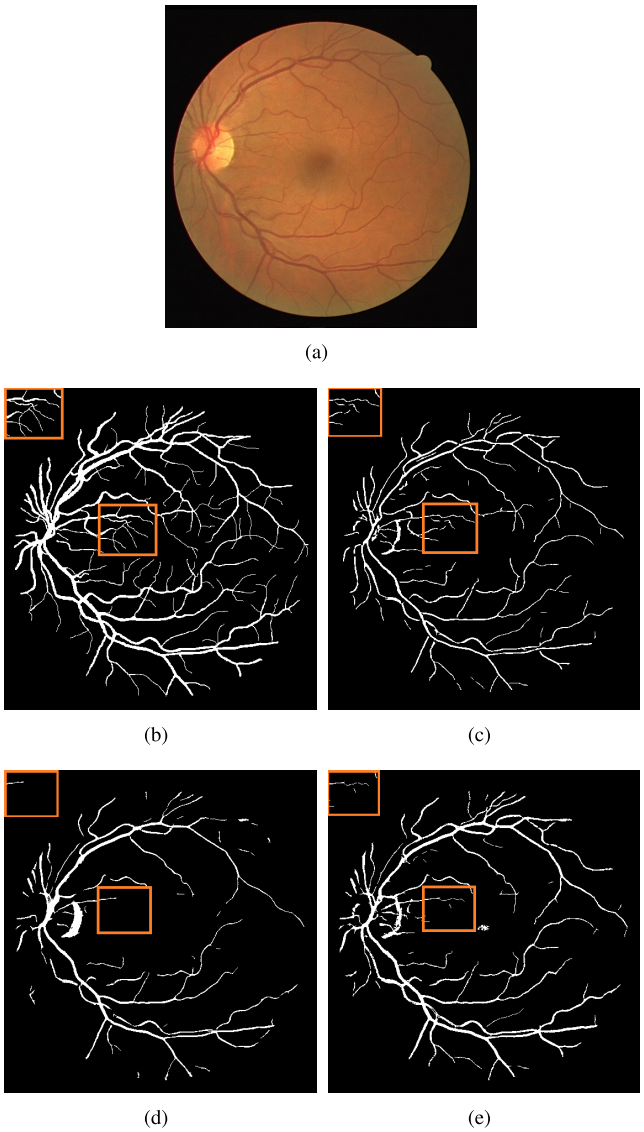

FIGURE 2. The detected retinal vascular structures by using different enhancement methods, compared with the specialist labelled ground truth vessel structures. (a): Original image. (b): Ground truth. (c): Our method. (d): Jerman's [20]. (e): MFAT [23].

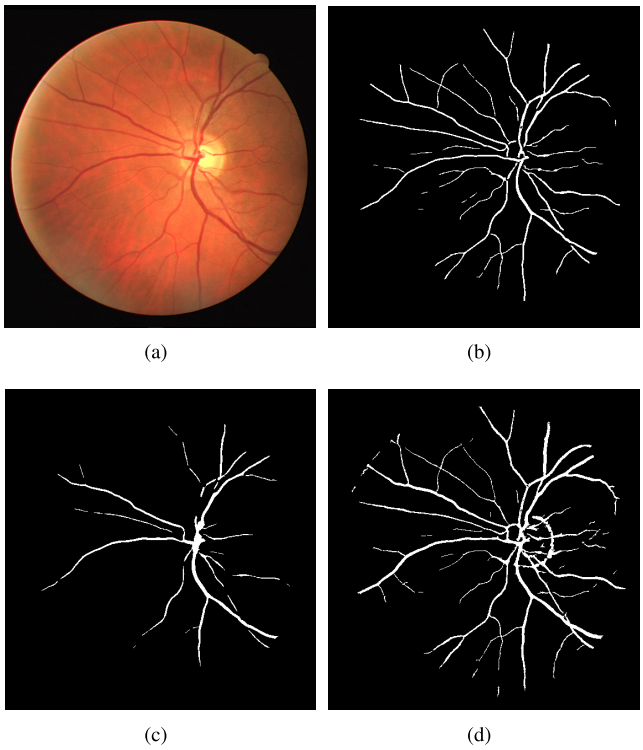

FIGURE 3. A comparison of the intermediate retinal vascular results of the proposed vesselness enhancement filter. (a): Original image. (b): Vessel enhancing diffusion only. (c): Improved vesselness filter only. (d): Our hybrid strategy.

TABLE 2. Segmentation results on 2013 vascusynth sample (%).

Data Set	TP	FN	FP	OM
1	98.14	1.86	3.43	98.30
2	96.52	3.48	6.18	95.84
3	96.13	3.87	6.82	95.58
4	95.87	4.13	7.31	95.29
5	96.96	3.04	4.09	96.81
6	96.90	3.10	5.58	96.73
7	97.46	2.54	4.75	96.92
8	96.59	3.41	6.19	95.70
9	97.45	2.55	4.37	97.16
10	97.53	2.47	5.15	97.24
Avg. ± std	96.96 ± 0.70	3.04 ± 0.70	5.39 ± 1.25	96.56 ± 0.94

B. 3D SYNTHETIC VASCULAR MODELS

In this stage, the segmentation approach is tested on the March 2013 VascuSynth Sample (10 datasets) presented in [30], [31]. Synthetic vascular trees of multiple complexities were generated by using the VascuSynth Software, by changing the number of terminal nodes from 5 to 1000 within a volume of 100 × 100 × 100 voxels [30]. Figure 4 presents three examples of synthetic vessel models from the March 2013 VascuSynth Sample: Group 2 (data3), Group 3 (data4) and Group 4 (data5), which are used as the ground truth vessel structures and adequate to represent the three dimensional vascular structures, for the purpose of evaluating the efficiency of the proposed vesselness filter function.

As reported in [31], four different quantitative metrics, i.e., true positives (TP), false negatives (FN), false positives (FP) and overlap measure (OM) between the detected vascular structures and the ground truth vessel segmentation, are computed for the synthetic validation. The average TP, FN, FP, and OM rates on the 10 datasets are presented in Table 2. The proposed method is found to achieve 96.96 ± 0.70, 3.04 ± 0.70, 5.39 ± 1.25 and 96.56 ± 0.94 percentage of TP, FN, FP, and OM rate for all 10 datasets, respectively. Moreover, low level of noise was added to the 2011 VascuSynth Sample Data [30], [31], and the proposed method was tested compared with Jerman's method [20] and the Multiscale Fractional Anisotropy Tensor (MFAT) method [23]. The comparison results are presented in Table 3. It can be seen that the proposed method can obtain the highest values for TP and OM, and lowest values for FN and FP, which demonstrates that the proposed method slightly outperforms

TABLE 3. A comparison of the multiscale fractional anisotropy tensor (MFAT) method, jerman's method with our method in the presence of low level of gaussian noise ($\sigma^2 = 20$) (%).

	TP			FN			FP			OM		
	MFAT [23]	Jerman's [20]	**Ours**	MFAT [23]	Jerman's [20]	**Ours**	MFAT [23]	Jerman's [20]	**Ours**	MFAT [23]	Jerman's [20]	**Ours**
Data1	93.38	94.26	**95.59**	6.62	5.74	**4.41**	7.46	7.10	**6.93**	93.73	93.92	**94.16**
Data2	93.87	94.45	**95.26**	6.13	5.55	**4.74**	5.38	5.06	**4.58**	94.65	94.78	**94.79**
Data3	94.29	95.17	**96.27**	5.71	4.83	**3.73**	5.73	5.04	**4.84**	95.09	95.41	**95.71**

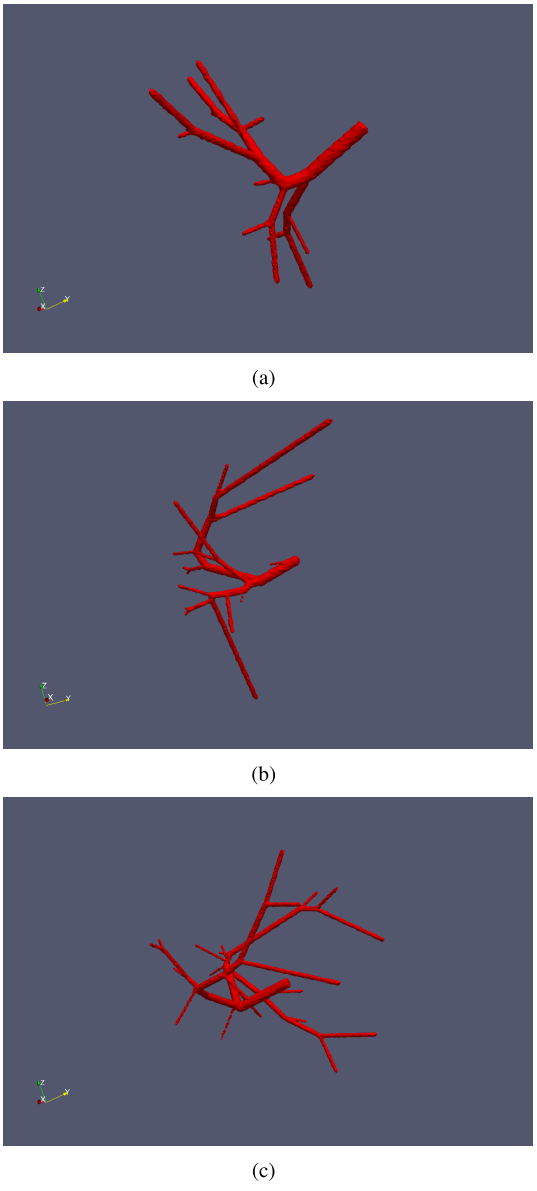

FIGURE 4. Three 3D examples of synthetic vessel models from the march 2013 vascusynth sample: Group 2 (data3), group 3 (data4) and group 4 (data5).

MFAT method and Cheng's method, with the presence of low level Gaussian noise.

Figure 5 presents a comparison of average true positives (TP), false negatives (FN), false positives (FP) and overlap measure (OM) measures by using Jerman's, MFAT and the proposed method on 2013 VascuSynth Sample. The new method is found to achieve the highest overlap measure. In addition, the statistical tests between the proposed method and the advanced methods (Jerman's method and MFAT method) are performed. The results (p-values < 0.05) indicate that there is a statistically significant difference between the proposed method and the advanced methods (Jerman's method or MFAT method). Figure 6 shows the maximum intensity displays (MIP) of three 3D synthetic vessel models from the March 2013 VascuSynth Sample by using different vessel enhancing methods, Frangi's (first column), Jerman's (second column), MFAT (third column) and the proposed method (last column). The proposed method shows better filtered vascular structures, especially for thin vessel branches.

TABLE 4. Dataset size and processing time by different vessel enhancing approaches of five real patient CCTA datasets, dataset 01 LAD, dataset 01 LCX, dataset 01 RCA, dataset 02 LAD and dataset 02 LCX.

	Size	Resolution (mm^3)	Time (min)		
			Jerman's	MFAT	Ours
ccta 1 LAD	201×200×169	0.439×0.439×0.25	15	17	**13**
ccta 1 LCX	201×200×83	0.4×0.4×0.25	9	10	**7**
ccta 1 RCA	201×200×143	0.31×0.31×0.25	13	14	**11**
ccta 2 LAD	201×200×169	0.319×0.319×0.3	14	16	**12**
ccta 2 LCX	201×200×67	0.319×0.319×0.3	8	9	**6**

C. APPLICATION TO PATIENT STUDY

In this section, the proposed vessel filter is implemented on five real patient CCTA datasets, which were obtained from the National Heart Center Singapore, and each ground truth artery, i.e., the left anterior descending artery (LAD), the left circumflex artery (LCX) and the right coronary artery (RCA), was labelled by the experienced cardiologist. The dataset size and processing time by using different vessel enhancing approaches of each group of data is summarized in Table 4. The proposed enhancing approach is proven to be efficient, with an average processing time of about 9.8 minutes. This enables the proposed diffusion scheme to be further applied as a real-time medical images preprocessing tool in clinical practice.

To explore the performance of the proposed vessel enhancing scheme, five other vascular enhancement methods (Frangi's, Yang's [21], VED, Jerman's and MFAT) were also performed into five CTCA datasets. Figure 7 depicts

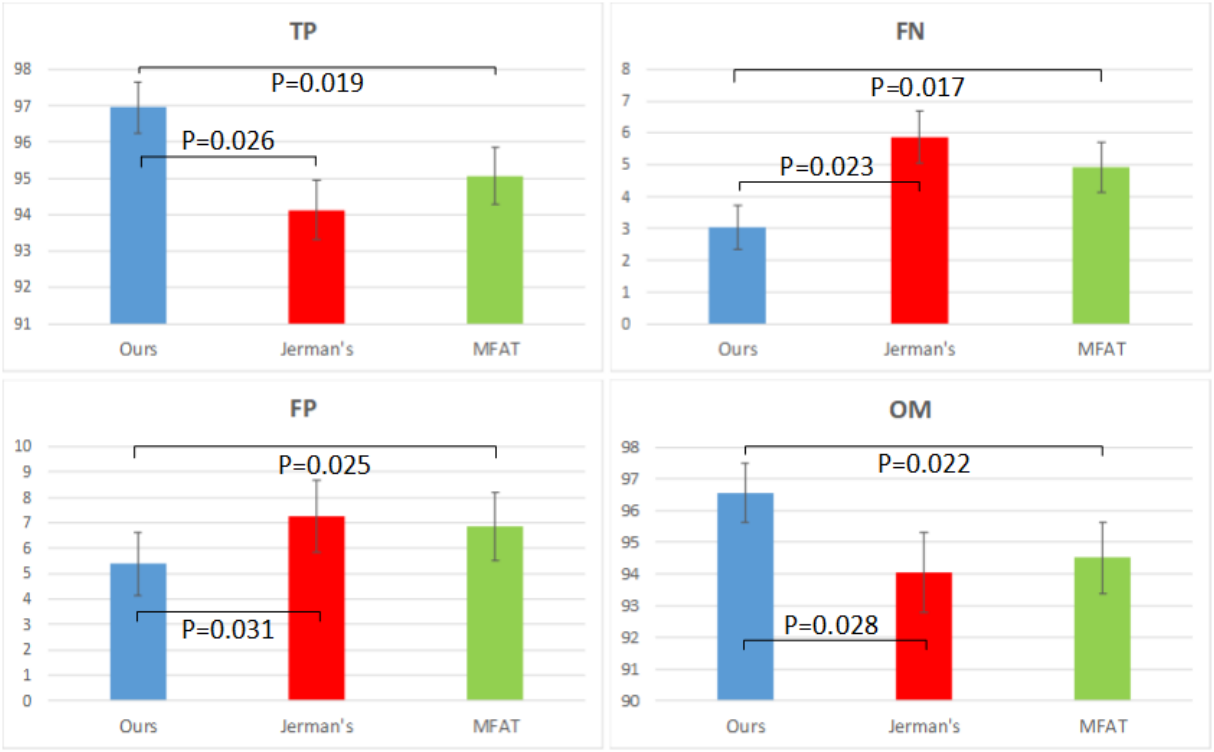

FIGURE 5. A comparison of average true positives (TP), false negatives (FN), false positives (FP) and overlap measure (OM) measures by using jerman's, MFAT and the proposed method and their p-values on 2013 vascusynth sample.

the comparison of the ROC curves for all the approaches. Frangi's filter achieves the lowest mean AUC value. This may be explained by the fact that Frangi's filter is sensitive to noise. Yang's improved filter achieves low value of AUC. VED is found to outperform the two latter methods. This is can be explained by the fact that VED utilizes the vesselness measure to construct the diffusion tensor. Jerman's method and the MFAT method can achieve higher AUC values. The proposed method is found to outperform the five existing state-of-the-art vessel enhancement methods, with the highest AUC value of 0.897.

In Figure 8 we present a visual comparison of the segmentation results in axial view obtained by using the MFAT method [23] and the proposed enhancement filter with the ground truth regions, for dataset 01 LAD, dataset 01 LCX and dataset 02 LCX. The first column (blue) shows the ground truth regions labelled by the professional cardiologist. The second column (yellow) gives the segmentation results by the MFAT method. The segmentation results obtained by using the proposed vesselness filter are presented in the last column (red). The experimental results demonstrate that the proposed vascular enhancement approach is capable of preserving more coronary artery features and reducing pseudo vessel structures. As a result, the segmentation results are more precise and reliable for clinical diagnosis.

IV. DISCUSSIONS

Vessel enhancement technique has been widely used as a common prerequisite in biomedical imaging before vessel segmentation and centerline detection, which provides important pathological information. Among the reviewed vessel enhancing approaches, the Frangi's filter is widely used, since it is easy to implement, and returns very high response uniformity on objects with uniform intensities. Besides, some improved vesselness filters are developed. They are usually modified from Frangi's function, like Yang's method [21], and can obtain only minor improvement on vascular structures detection. Non-linear anisotropic diffusion filtering can take place in certain structure direction since it uses the information of the structure tensor orientation. Hence, they are able to preserve important features during the filtering process. However, diffusion based methods are not capable of detecting vessels within a wide range of scales, since they act at a fixed size. Moreover, diffusion tensors, like the Fractional Anisotropic Tensor (FAT), have been widely used to advance the detection of vascular structures. FAT has great potential in medical images processing, like diffusion tensor regularization. However, the method introduces too many parameters and threshold values, which makes it difficult to be used for other medical datasets.

In this work, we develop a hybrid technique for fast and accurate vascular enhancement filter, which contains two main steps: vesselness diffusion and improved vesselness filter based on the eigenvalues ratio. The diffusion tensor proposed in this work is controlled by the image structure tensor. As a result, the main diffusion takes place along the vessel direction of the underlying image. For ideal tubular structures, the diffusion process guarantees that the diffusion

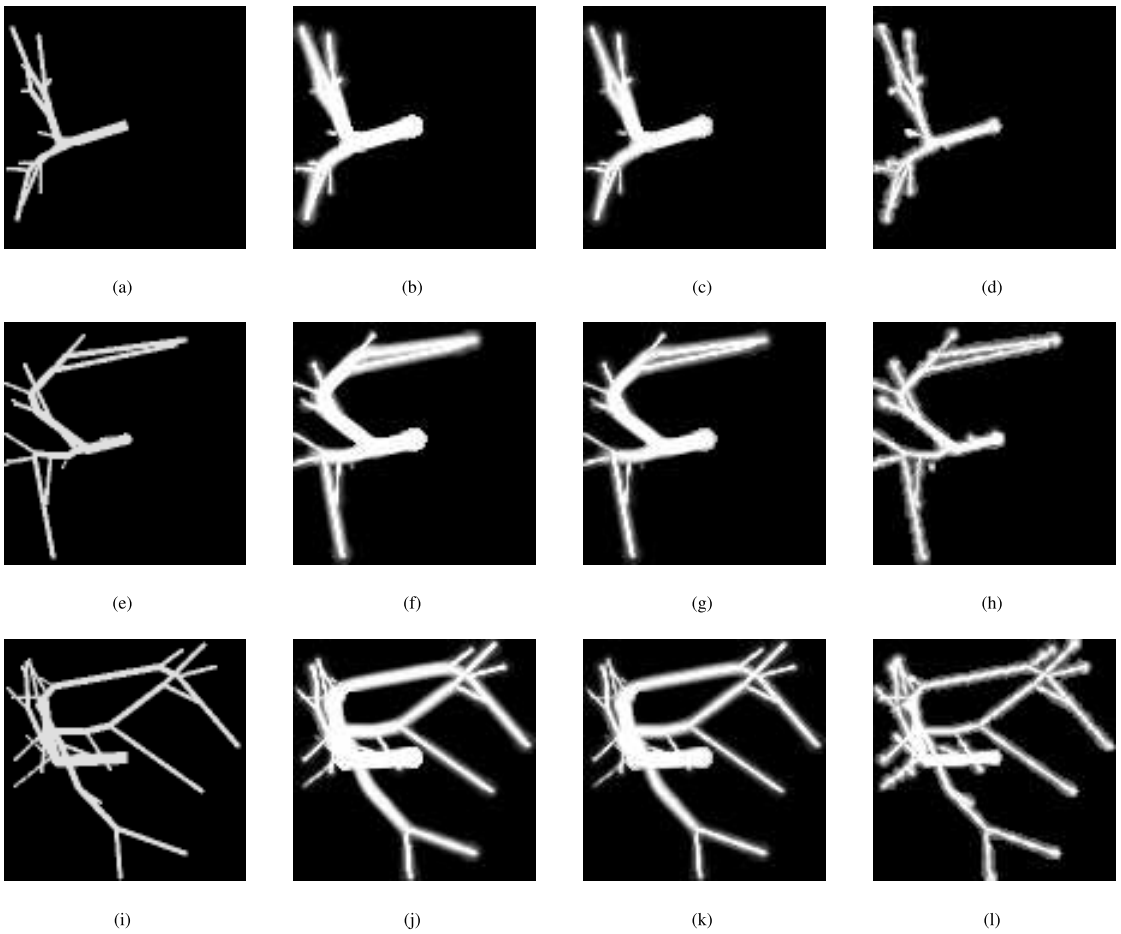

FIGURE 6. Maximum intensity displays (MIP) of three 3D synthetic vessel models from the march 2013 vascusynth sample: Group 2 (data3), group 3 (data4) and group 4 (data5), by using different vessel enhancing methods, frangi's (first column), jerman's [20] (second column), MFAT [23] (third column) and the proposed method (last column).

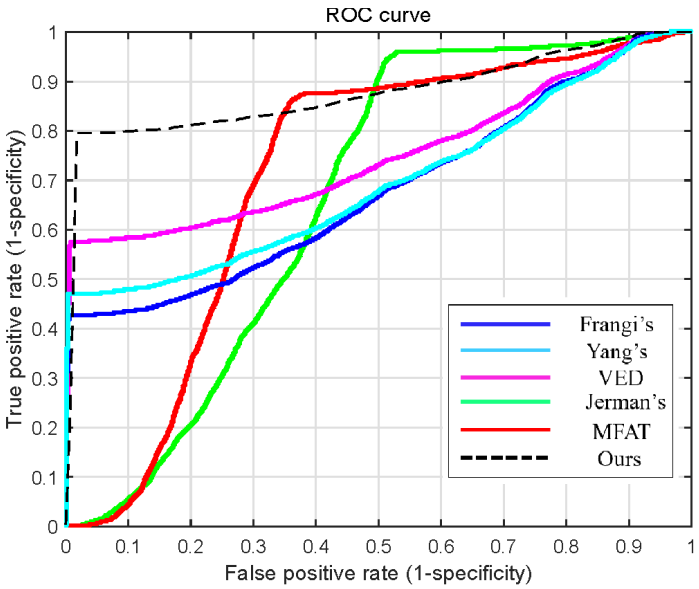

FIGURE 7. A comparison of the ROC curves for all the approaches.

strength is maximal and hence thin vessels can be preserved. For non-vessel structures, the diffusion strength is isotropic and high and noises can be removed. The proposed vesselness enhancement diffusion algorithm is designed for medical images including vascular structures, which can be viewed as a pre-processing technique before vessel segmentation

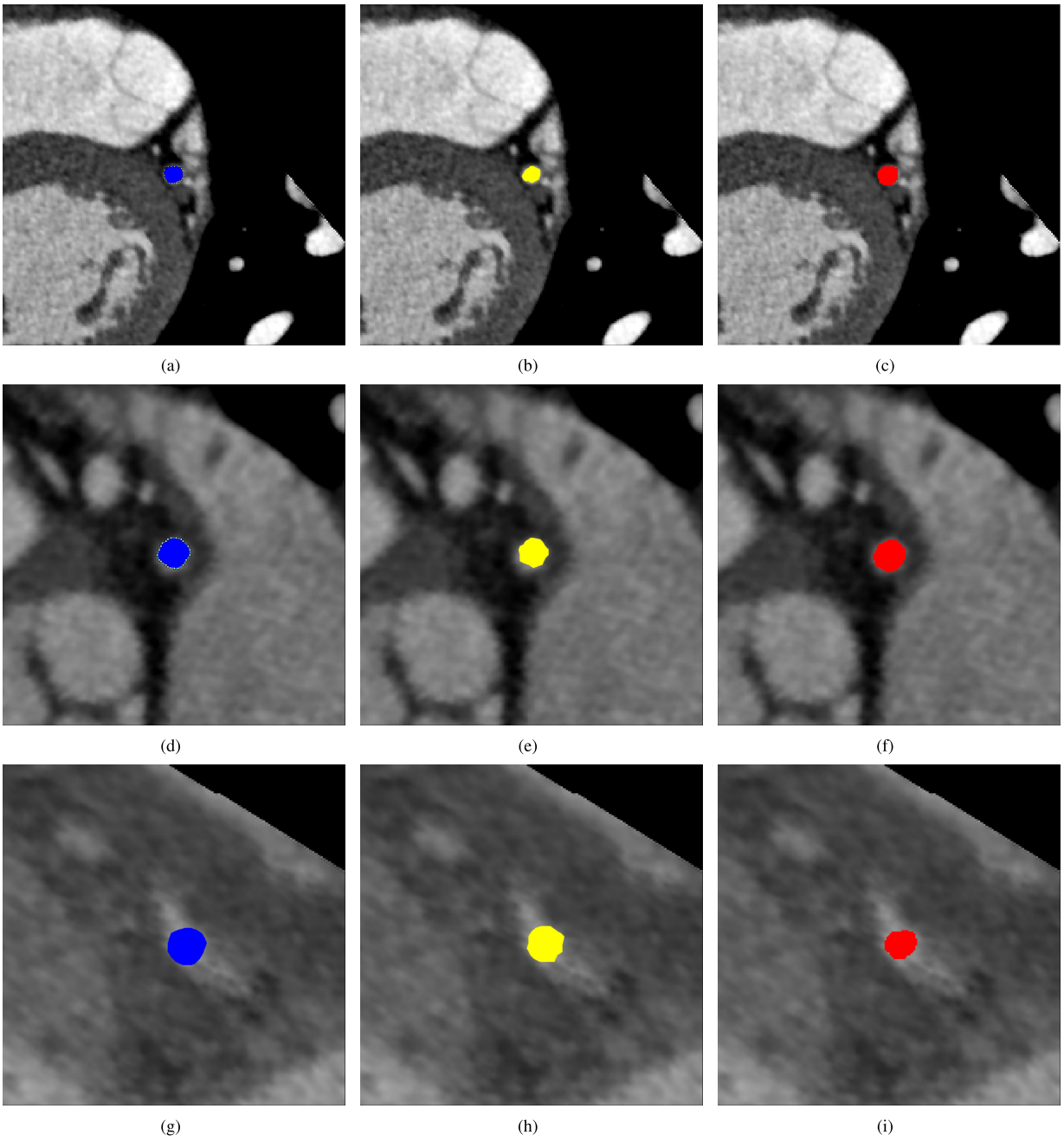

FIGURE 8. A visual comparison of the segmentation results obtained by using the MFAT method [23] (yellow) and the proposed enhancement filter (red) with the ground truth regions (blue) in axial view. First row: Dataset 01 LAD. Second row: Dataset 01 LCX. Third row: Dataset 02 LCX.

and centerline extraction. The Frangi's filter is modified by multiplying a term, in order to make the derivatives of the vesselness measure smooth at the origin and allow it to be used in the diffusion equation. However, the term needs to be carefully selected. Moreover, the parameters of the diffusion procedure can also be further explored to produce better diffusion results in the further work. Once original images is filtered by the proposed diffusion algorithm, the Hessian matrix at each voxel location is computed, and the eigensystem is further explored. An improved vesselness filter function can be designed in the form of the ratio of eigenvalues. The filter is not proportional to any eigenvalue and, at the same time, is robust to low-magnitudes of the eigenvalues. Compared with vesselness filters of other forms, this type of vesselness filter has two main advantages. First, it returns a response that is close-to-uniform. Second, it enables that the response is invariant to object contrast. These two advantages play an utmost role in balanced and accurate vesselness enhancement.

Finally, the proposed vascular structures enhancement method may garner a high potential in clinical practice, since it may also enhance vascular structures with non-circular

cross sections (at lesion areas). For vessels in the presence of vascular disease, $\mathcal{V} < 1$, the parameter ω works on λ_1' in (16) and guarantees that the diffusion strength is still high. Thus even vessels with lesion sites can be well preserved. This is because the proposed vesselness diffusion takes place in certain structure direction since it uses the information of the structure tensor orientation. Therefore, it is able to preserve important features during the filtering process. In our future work, we are going to explore the performance improvement of the existing segmentation and reconstruction approaches, which rely on prior vascular structures enhancement results.

V. CONCLUSION

In this study, we developed a hybrid vesselness filter for vascular structures enhancement from noisy medical images, which takes the advantages of vesselness enhancement diffusion, and integrates the improved Frangi's filter based on the ratio of eigenvalues of the Hessian matrix. We have first modified the original Frangi's vesselness filter by multiplying an exponential term to make it smooth at the origin. Based on this, a novel diffusion tensor can be constructed, and original medical images can be processed, in order to enhance vascular structures and inhibit surrounding noises. Second, the Hessian matrix was computed and the novel vessel enhancing filter was then developed based on the eigenvalues ratio. This novel approach has been validated over the public 2D retinal datasets and 3D synthetic vascular structure models. It showed that the the novel method can detect more thin retinal vessel branches by a visual comparison. Besides, the AUC value of the ROC curve of the proposed method was further compared with that of each state-of-the-art approach, and the new method gave the highest AUC value. In addition, the new method can achieve highest AUC value on the March 2013 VascuSynth Sample and the 2011 VascuSynth Sample with low level of noise. Experimental results demonstrate that the proposed filter outperforms other existing approaches for curvilinear structure enhancement from noisy images. Moreover, the novel approach is further evaluated on real patient Coronary Computed Tomography Angiography (CCTA) datasets with ground truth regions labelled by professional cardiologist. Our method is proven to produce more accurate coronary artery segmentation results. Given the accuracy and efficiency, the proposed vesselness filter should have more routine clinical applicability as a real-time vascular structures enhancement tool before vessel segmentation and quantification.

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