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3D Shape Modeling and Analysis of Retinal Microvasculature in OCT-Angiography Images

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Abstract

3D optical coherence tomography angiography (OCT-A) is a novel and non-invasive imaging modality for analyzing retinal diseases. The studies of microvasculature in 2D *en face* projection images have been widely implemented, but comprehensive 3D analysis of OCT-A images with rich depth-resolved microvascular information is rarely considered. In this paper, we propose a robust, effective, and automatic 3D shape modeling framework to provide a high-quality 3D vessel representation and to preserve valuable 3D geometric and topological information for vessel analysis. Effective vessel enhancement and extraction steps by means of curvelet denoising and optimally oriented flux (OOF) filtering are first designed to produce 3D microvascular networks.

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Afterwards, a novel 3D data representation of OCT-A microvasculature is reconstructed via advanced mesh reconstruction techniques. Based on the 3D surfaces, shape analysis is established to extract novel shape-based microvascular area distortion via the Laplace-Beltrami eigen-projection. The extracted feature is integrated into a graph-cut segmentation system to categorize large vessels and small capillaries for more precise shape analysis. The proposed framework is validated on a dedicated repeated scan dataset including 260 volume images and shows high repeatability. Statistical analysis using the surface area biomarker is performed on small capillaries to avoid the effect of tailing artifact from large vessels. It shows significant differences ($p < 0.001$) between DR stages on 100 subjects in a OCTA-DR dataset. The proposed shape modeling and analysis framework opens the possibility for further investigating OCT-A microvasculature in a new perspective.

Keywords

Optical coherence tomography angiography; Diabetic retinopathy; Retinal microvasculature; Shape analysis

I Introduction

Optical coherence tomography angiography (OCT-A) is a non-invasive 3D imaging modality that provides a cross-sectional view of high-contrast microvascular details with micrometer-scale depth resolution. It has been increasingly taken as a valuable imaging tool to observe retinal vascular changes in eye-related diseases like diabetic retinopathy (DR), age-related macular degeneration (AMD), and retinal arterial/venous occlusion [1].

Many studies [1], [2] have been performed on various retinal imaging modalities to analyze vascular changes. A comprehensive overview of technical and clinical studies is provided by Kashani *et al.* [1] to show the great promise of using OCT-A to analyze multiple diseases like glaucomatous optic neuropathy, DR, AMD, uveitis and macular telangiectasia type 2. Among those studies [3]–[7], 2D *en face* OCT-A representation is often used for structural analysis due to its high-contrast capillary details for illustrating clinically-relevant findings. By extracting microvascular structures from different OCT-A depth layers, one can obtain their corresponding *en face* projections to analyze respective variations [8]–[10]. Kim *et al.* [4] and Jia *et al.* [11] quantified the capillary loss between normal and non-proliferative diabetic retinopathy (NPDR) subjects on *en face* OCT-A data to show its effectiveness in describing DR severity when compared with other image modalities. They also took advantage of the nice three-dimensional property of OCT-A with separation of *en face* visualizations at different depth layers to evaluate retinal vascular abnormalities of several diseases. To distinguish glaucoma from healthy eyes, Richter *et al.* [6] extracted important microvascular biomarkers from the macular and peripapillary regions in OCT-A images and they found that peripapillary perfusion parameters show better significance. Kim *et al.* [5] employed different measures such as skeleton density, vessel density and fractal dimension in OCT-A to quantify retinal microvascular changes in uveitis. These works show that 2D *en face* representation of OCT-A provides clinicians with important information for analyzing

OCT-A images. However, geometric and topological properties from the original 3D microvasculature including rich depth information can be inevitably obscured in 2D space.

In practice, high-quality 3D OCT-A vessel visualization can be very helpful to clinicians for observing microvascular changes. 3D volume rendering techniques have been described to view 3D microvascular representation. Spaide *et al.* [12] exploited 3D volume rendering of OCT-A to investigate vascular abnormalities in diabetic macular edema. They also utilized it to qualitatively evaluate retinal vascular changes associated with macular telangiectasia type 2 [13]. These findings show that 3D volume rendering is better at presenting the depth information of vessel abnormalities, but it does not allow quantitative and automatic analysis of the full microvascular networks [1]. In this work, we therefore aim to a comprehensive 3D OCT-A microvascular shape modeling and analysis framework to enable automated and large-scale 3D OCT-A studies. On one hand, our framework is able to produce a novel 3D surface-based microvascular visualization to assist ophthalmologists. On the other hand, it provides rich geometric and topological information for the quantitative analysis of OCT-A microvasculature from a new perspective.

We first propose to design a surface-based shape modeling process for 3D microvascular data representation. The surface reconstruction is often used in brain imaging studies [14]–[17] to measure cortical morphometry and tissue integrity. Here, we for the first time establish a high-quality 3D OCT-A vessel surface representation for dedicated microvascular shape analysis. Before surface reconstruction, a complete microvascular network with well-segmented vessel boundary masks needs to be extracted from each OCT-A image. This requires an effective method for accurate 3D microvascular extraction. Similar vessel enhancement and segmentation tasks have been performed on 2D retinal color fundus photography, fluorescein angiography and OCT images [18]–[22], but no available method is specifically designed for processing large-scale 3D OCT-A data due to their high complexity and low capillary visibility. To this end, a 3D vessel enhancement approach is designed to preserve capillary continuity and highlight complex microvascular details by adapting the curvelet transform and optimally oriented flux (OOF) techniques [23], [24]. Then, the binarized vessel boundary masks are extracted for 3D surface reconstruction. To ensure the boundary of the vessel mask is a valid surface, we include a boundary correction process to achieve well-composedness [25]. This process is also integrated with Laplacian smoothing and topology preservation to achieve a smooth surface representation without outliers.

Based on the surface representation, we aim to characterize complex microvascular variations using intrinsic 3D shape analysis. The OCT-A microvasculature includes large vessels and small capillaries, which provides rich geometric and topological information for further disease studies [26], [27]. However, the tailing artifact [28]–[31], which is mainly located on large vessels and connected with “real” blood flow signals, can bring confounding factors to subsequent biomarker extraction and make the final diagnosis less reliable. To avoid that, we design a novel shape analysis framework by exploring intrinsic surface-based geometry to classify large vessels and small capillaries on triangular surfaces separately. As such, a surface-based area distortion measure is defined as a representative feature via Laplace-Beltrami (LB) eigen-projection on triangular meshes for a graph-cut

based surface segmentation. This gives the possibility for analyzing small capillaries independently without being affected by tailing artifact on large vessels. In addition, surface-based biomarker analysis is established to show the great potential of extracting useful quantitative shape-based OCT-A vessel biomarkers for disease assessment.

The proposed shape modeling framework is validated on a dedicated OCT-A repeated scan (RS) dataset including 260 volume images and shows high effectiveness and repeatability. We also evaluate the shape analysis framework by calculating the surface area biomarker separately on large vessel and small capillaries from a clinical DR dataset with 100 subjects. Significant differences are found by performing statistical analysis between surface areas and three DR stages. The main contributions can be summarized as follows.

- i. The proposed framework is able to produce a novel and high-quality 3D OCT-A microvascular visualization which has not been previously demonstrated and may provide a unique tool for clinical and scientific analysis.
- ii. A novel 3D surface-based framework is designed for OCT-A vessel shape modeling and analysis. We take advantage of the detailed depth-resolved 3D microvascular information that has rarely been used in OCT-A analysis.
- iii. To achieve a smooth shape representation of the highly tortuous retinal vessels, we develop a novel iterative procedure based on area distortions to detect and remove spurious geometric outliers in 3D OCT-A microvascular surfaces.
- iv. We categorize large vessels and small capillaries by employing our novel OCT-A shape analysis for more specific 3D surface-based microvascular study.
- v. In addition to the theoretical framework, we also give a full evaluation/benchmarking of our method via a well-established 3D OCT-A repeated scan dataset and a clinical DR dataset. This shows the proposed framework is effective and repeatable as a potentially valuable tool in retinal imaging research.

II. 3D Microvascular Surface Reconstruction

In Fig. 1, we summarize the proposed shape modeling and analysis framework consisting of four main processing phases. In this section, we will explain the main steps in the reconstruction of the novel 3D OCT-A microvascular surface representation.

A. 3D OCT-A Microvascular Enhancement

Low signal-to-noise ratio (SNR) is a common issue in OCT(-A) images [1], [22], and causes processing difficulties due to poor image quality and low vessel visibility. In particular, the 3D complex microvasculature and dense capillaries with disconnections bring challenges for accurate vessel extraction. As such, image enhancement module has been designed in our recent development [32] to reduce noise level and recover vessel continuity in OCT-A images. We employ the curvelets model [23] for OCT-A denoising since it not only considers local features in a multi-scale level but also makes use of the structure direction information. In this work, we employ the curvelet tools from the Curvelab¹ to transform a 3D volume image to curvelet domain and then process the obtained coefficients

correspondingly. The curvelet denoising technique provides the flexibility to adapt the coefficients thresholding parameters based on varying image quality and noise characteristics. In this step, we avoid excessive denoising effects to preserve useful OCT-A capillary details with good continuity for subsequent vessel enhancement. A global threshold value of 15 is empirically chosen here to truncate the curvelet coefficients. In Fig. 2(b) we can see that the background noise is significantly suppressed and high-quality perceptual continuity is achieved with preserved capillary connections.

Multi-scale and multi-orientation curvilinear enhancement methods like Hessian-based filters [19], [33] have been widely used to enhance vessel structures in medical images. The anisotropic OOF [24] was designed to compute the vesselness map of curvilinear structures at their optimal scales. One main advantage of the OOF is that it excludes the region in the neighborhood of a structure where extra structures may exist. This makes it suitable for distinguishing between closely located adjacent OCT-A vessels in dense microvascular networks. The OOF is a quadratic function defined on a symmetric matrix $\mathcal{Q}(\mathbf{x}, r)$ that can be decomposed as $\mathcal{Q}(\mathbf{x}, r) = \sum_{i=1}^3 \lambda_i(\mathbf{x}, r) \vec{v}_i(\mathbf{x}, r) \vec{v}_i(\mathbf{x}, r)^T$ using eigenvalues $\lambda_i(\mathbf{x}, r)$ and eigenvectors $\vec{v}_i(\mathbf{x}, r)$ in a local spherical region with radius r , where $\mathbf{x} = (x, y, z) \in \mathbb{R}^3$. Since the OCT-A vessel voxels have intensity values higher than background voxels, one has $\lambda_1(\cdot) \ll \lambda_2(\cdot) \ll \lambda_3(\cdot) \approx 0$ inside vessels. In 3D OCT-A images, the first two eigenvectors $\vec{v}_1(\cdot)$ and $\vec{v}_2(\cdot)$ span the normal plane of the vessel structure and the third eigenvector $\vec{v}_3(\cdot)$ indicates the vessel direction. Then, we define the final 3D OCT-A vesselness map for each voxel as $\mathcal{P}(\mathbf{x}) = \max \left\{ \max_r \left\{ -\frac{1}{r^2} \lambda_1(\mathbf{x}, r) \right\}, 0 \right\}$ by exploiting the negative eigenvalue with the largest magnitude. The obtained vesselness map $\mathcal{P}(\mathbf{x})$ has very high responses for vessel voxels and very low responses for background voxels. In this work, one of our prime interests is to investigate the smallest retinal vessels, called capillaries, of the retinal microvasculature. Hence, we pay special attention to the enhancement of capillaries where low intensities and weak connections are presented. In Fig. 2(c), we show results of the OOF-based OCT-A vessel enhancement. The final binary segmentation map $\mathcal{B}(\mathbf{x})$ is obtained by rescaling the vesselness map between 0 and 1 and then giving a suitable threshold value $T_{\mathcal{P}}$.

B. Well-Composedness of Vessel Mask Boundary

In this work, our prime interest is to analyze the rich microvasculature located in the superficial and deep retinal slabs (as shown in Fig. 3). To this end, the retinal layer boundaries in all OCT volumes were specifically annotated using the publicly available OCT-Explorer software [34]. Thereby we can generate a mask to define the volume of interest (VOI) for the superficial and deep retinal slabs. Throughout this work, the proposed 3D shape modeling and analysis framework is performed in this defined VOI for microvascular study.

¹A C++/Matlab toolbox available from CurveLab (www.curvelet.org)

The OCT-A image volume size is $245 \times 245 \times 1024$ sampled respectively in the x - y - z directions in an area of $3\text{mm} \times 3\text{mm} \times 2\text{mm}$. See Fig. 3. The width of capillaries in the x - y plane of OCT-A images are in general represented by around 1~4 voxels due to limited image resolution. This factor causes that many neighborhood voxels are not well-connected in the binary segmentations. To perform the subsequent shape analysis, the vessel boundary surface is required to be a manifold with useful geometric and topological properties. To this end, the well-composedness property [25] of the segmented microvascular masks need to be satisfied. However, this is not always valid in arbitrary masks across a large dataset. To ensure the well-composedness, we introduce perturbations by employing the boundary correction tool *mri_jretess* in Freesurfer [35] to improve the binary segmentations for a smooth vessel boundary surface reconstruction. In Fig. 2(d), we can see that several locations are filled with voxels (in green color) to satisfy the well-composedness condition.

C. 3D Mesh Surface Reconstruction with Outlier Removal

We focus on designing a specific surface reconstruction module for smooth shape representation of OCT-A microvasculature. This module involves two main phases. In the first phase, we establish a complete triangular surface representation based on the well-composed 3D binary vessel mask $\widehat{\mathcal{B}}(\mathbf{x})$ which is defined over a lattice of grid points $A = \{(i, j, k) \in \mathbb{Z}^3 \mid 0 \leq i < N_x - 1, 0 \leq j < N_y - 1, 0 \leq k < N_z - 1\}$, where we define the spatial dimensions $N_x = N_y = 245$ and $N_z = 1024$ for our clinical OCT-A data. The voxel points A can be further divided into two categories: vessel voxels which are represented by $A_v = \{(i, j, k) \in A \mid \widehat{\mathcal{B}}(i, j, k) = 1\}$, and background voxels which are denoted by $A_b = A \setminus A_v$. We assign a rectangular cuboid $\mathcal{C}(\mathbf{p})$ centered around each grid point $\mathbf{p} = (i, j, k) \in A_v$. The cuboid $\mathcal{C}(\mathbf{p})$ is given by

$$\mathcal{C}(\mathbf{p}) = \{(x', y', z') \in \mathbb{R}^3 \mid |x' - ih_{x'}| \leq \frac{h_{x'}}{2}, |y' - jh_{y'}| \leq \frac{h_{y'}}{2}, |z' - kh_{z'}| \leq \frac{h_{z'}}{2}\}, \quad (1)$$

where $h_{x'}$, $h_{y'}$ and $h_{z'}$ are determined by the spatial sampling size during the OCT-A imaging process in the x' , y' and z' directions, respectively. Then a set of rectangular faces $\mathcal{R} = \{\mathcal{R}_1, \mathcal{R}_2, \dots, \mathcal{R}_{N_{\mathcal{R}}}\}$ on the boundary between vessel region A_v and background region A_b are defined by taking the intersection of the cuboids $\mathcal{C}(\mathbf{p}) \cap \mathcal{C}(\mathbf{q})$ of two voxels $\mathbf{p} \in A_v$ and $\mathbf{q} \in A_b$ [16]. Afterwards, the continuous surface representation is obtained by numerically dividing each rectangular face into two triangular faces as shown in Fig. 4(a)-(b). The triangular mesh surface $\mathcal{M}$ is represented by vertices and triangular faces, i.e. $\mathcal{M} = \{\mathcal{V}, \mathcal{T}\}$ where $\mathcal{V} = \{\mathcal{V}_i \mid i = 1, \dots, N_{\mathcal{V}}\}$ and $\mathcal{T} = \{\mathcal{T}_j \mid j = 1, \dots, N_{\mathcal{T}}\}$ denote the set of vertices and triangles, respectively. For any given triangular face $\mathcal{T}_j$ with its three vertices on surface, we can always map it to the corresponding voxels. This enables the freedom to move between the continuous surface and discrete volume representations for further processing.

In the second phase, an efficient shape analysis based evolution module is developed to remove geometric outliers on the reconstructed microvascular surface. The vessel segmentation and mesh reconstruction performance on complex microvasculature in 3D OCT-A images are often affected by non-smooth vessel boundaries and geometric outliers. As shown in Fig. 4(c), geometric outliers like surface protrusions in *cusp* and *wedge* shapes are generated during the surface evolution process on vessel boundary masks. Those issues need to be solved in order to achieve a smooth and clean vascular surface representation. To filter out those outliers, Laplacian smoothing is employed to efficiently quantify the changing ratios of triangular faces on spurious geometric outliers. The distortion metric for reflecting the surface area changing ratio is defined by taking the fraction of the original triangular face area size over the smoothed area size. Specifically, each mesh vertex $\mathcal{V}_i$ is smoothed by following

$$\mathcal{V}'_i = \alpha \mathcal{V}_i + (1 - \alpha) / N_r \sum_{j=1}^{N_r} \mathcal{V}_j, \quad (2)$$

where N_r denotes the number of adjacent vertices to the current vertex $\mathcal{V}_i$, and $\mathcal{V}_j$ is the j -th adjacent vertex, where $\mathcal{V}'_i$ represents the new position for the current vertex $\mathcal{V}_i$, and we use the weight parameter $\alpha = 0.7$ in our vessel smoothing case to balance the inclusion of the central position $\mathcal{V}_i$.

To remove the geometric outliers without affecting the boundary geometry of other parts, we iteratively detect the triangular faces where the area distortions are larger than a threshold value of 10. Those triangular faces are then transformed back to the corresponding locations in the discrete vascular mask representations in the lattice domain by following the boundary deformation procedure in [15]. In the new surface reconstruction iteration, those locations will be deformed in a way that the geometric outliers can be filtered out in the lattice domain. In Fig. 4(d), we can see a typical case showing that smooth microvascular surfaces are obtained after our outlier removal procedure. Then, extra geometric outliers like very small independent components with less than 5000 vertices are detected based on geodesic distances between vertices, and removed from the original mesh surface. In addition, some of the OCT-A microvascular structures have low visibility and thus may produce very thin connections in the segmented boundary mask. Even with limited surface evolutions, they may still result in excessive shrinkage and disconnections in those thin parts. To preserve vessel topology and continuity, mesh surface shrinkage are terminated at the locations where disconnection can happen after one more evolution. Finally, a complete triangular surface representation is established to model the 3D microvasculature from OCT-A.

III. Shape Analysis on 3D Microvascular Surfaces

In this section, shape analysis methods are developed to tackle the challenges in describing 3D OCT-A microvascular topology and geometry. Tailing artifact [28], [30] is one type of projection artifacts [1], [29] that connect with the “real” superficial blood flow signals and appear as a long tail downward on cross-sectional OCT-A. See Fig. 5 for an illustrative

example. The tailing artifact causes large vessel thickening in z -direction and produces many spurious vessel parts. Since the superficial anatomy includes predominantly radially oriented large vessels, their tailing artifacts will strongly affect the vessel topology and further biomarker analysis. Thus, we propose to segment and analyze small capillaries separately to avoid the influence of tailing artifacts from large vessels for 3D microvascular shape analysis.

A. Calculation of Area Distortion via Laplace-Beltrami (LB) Eigen-Projection

We aim to extract useful geometric features using shape analysis to support the subsequent graph-cut segmentation. The Laplace-Beltrami spectral analysis [15], [36] can reflect the intrinsic geometry of various surfaces for 3D shape comparison and analysis. The LB eigen-functions are calculated from the vascular surface without considering any parameterizations. They also own the nice property of being isometric invariant and as such are reliable models to deal with the boundary surfaces with jagged nature like OCT-A microvasculature. By using the LB eigen-analysis we can quantify the geometric differences between vessels. Based on the triangular mesh representation $\mathcal{M} = (\mathcal{V}, \mathcal{T})$, the LB eigen-system can be numerically computed by solving a matrix eigenvalue problem [15] $Qg = \lambda Kg$, where the two matrices Q and K are generated from the one-ring neighborhood of vertices, and where λ is the eigenvalue and g is the corresponding eigenfunction.

An intuitive observation in OCT-A is that the surface representation of neighboring triangular faces of large vessels with high thickness is more flat/smooth than that of small capillaries which are more tortuous, as shown in the triangular mesh of Fig. 6(c). If we define each coordinate of vertices as the feature function γ then the LB eigen-projection intrinsically describes the smoothness of the coordinate functions. Therefore, during eigen-projection, the triangular faces of large vessels will present less area distortions than those of small ones due to the smoothness of their vessel geometry. This motivates us to establish the vessel shape classification method using surface-based area distortions. Instead of performing the simple Laplacian smoothing, here we rely on the LB eigen-projection to obtain more precise shape representation of surface distortions. The eigenvalues and eigenvectors of the discrete LB eigen-system can be ordered as $0 = \lambda_0 < \lambda_1 < \lambda_2 < \dots$ and $g_0, g_1, g_2, \dots$, respectively. For surface segmentation, we define a feature function $\gamma: \mathcal{M} \mapsto \mathbb{R}$ at each vertex with the goal of classifying each vertex into large or small vessels. The eigen-projection onto the space of the first L eigen-functions is defined as

$$\hat{\gamma} = \sum_{l=0}^{L-1} g_l \int_{\mathcal{M}} \gamma g_l d\mathcal{M}, \quad (3)$$

where both the eigen-function g_l and the feature function γ are defined on vertices with vector size $N_{\mathcal{V}} \times 1$. The eigen-projection of γ can be written as

$$\hat{\gamma} = \mathcal{H}_L \mathcal{H}_L^T K_{\gamma}, \quad (4)$$

where $\mathcal{H}_L = [g_0 \ g_1 \cdots g_{L-1}]$ represents the first L eigen-functions and K considers the integral on mesh. For the coordinate $\mathcal{V}_i = (x'_i, y'_i, z'_i)$ of the i -th vertex on surface $\mathcal{M}$, its LB eigen-projection denotes the projected coordinate $\widehat{\mathcal{V}}_i = (\widehat{x}'_i, \widehat{y}'_i, \widehat{z}'_i)$ on the projected mesh surface $\widehat{\mathcal{M}} = (\widehat{\mathcal{V}}, \widehat{\mathcal{T}})$ where $\widehat{\mathcal{V}} = \{\widehat{\mathcal{V}}_i \mid i = 1, \dots, N_v\}$ and $\widehat{\mathcal{T}} = \mathcal{T}$. For each l -th triangle $\mathcal{T}_l$ on the original mesh $\mathcal{M}$, we can calculate its triangular face area by $\text{Area}(\mathcal{T}_l) = \frac{1}{2} d_{ij} d_{ik} \sin \theta_l^{jk}$, as shown in Fig. 6(e). Similarly, we can calculate $\text{Area}(\widehat{\mathcal{T}}_l)$ on the projected mesh $\widehat{\mathcal{M}}$. Hence, the area distortion ratio r_{AD} is specifically defined on each triangular face to quantify the geometric differences on large vessels and small capillaries:

$$r_{AD} = \text{Area}(\mathcal{T}_l) / \text{Area}(\widehat{\mathcal{T}}_l). \quad (5)$$

For the vessel mesh surface in Fig. 6(a), the area distortion ratio map is plotted in Fig. 6(b), where it has been normalized between 0 and 1. We can see that the area distortion ratios r_{AD} present low values below 0.6 in the mesh surfaces of large vessels, while it shows high values roughly above 0.6 in the surfaces of small capillaries. This indicates the potential of using the shape-based area distortion ratio r_{AD} to classify small capillaries from large vessels on surfaces. In Fig. 6(c), we show the classification result obtained by thresholding the area ratio map in Fig. 6(b) at $r_{AD} = 0.6$. We can observe that large vessel surfaces are roughly extracted from the whole mesh surfaces. However, there still exists inaccurate segmentation of small vessel surfaces (marked in blue region) in the classified result. To achieve more precise vessel surface categorization, we propose to employ the graph-cut segmentation technique to refine the extraction of capillary surfaces, such that large vessels and small capillaries can be more accurately classified with proper regularization.

B. Graph-Cut based Large and Small Vessel Classification

Based on the extracted area distortion ratio r_{AD} , we aim to classify all vertices of the OCT-A microvascular surfaces $\mathcal{M} = (\mathcal{V}, \mathcal{T})$ into two sets $\mathcal{D}_S$ and $\mathcal{D}_L$, for small capillaries and large vessels, respectively. The 3D surface segmentation can be achieved by considering it as a minimization problem with the following energy function

$$\begin{aligned} \varepsilon(\mathcal{D}_S, \mathcal{D}_L) = & - \sum_{\mathcal{V}_i \in \mathcal{D}_S} \log p_S(\gamma(\mathcal{V}_i)) - \sum_{\mathcal{V}_i \in \mathcal{D}_L} \log p_L(\gamma(\mathcal{V}_i)) \\ & + \lambda \sum_{i=1}^{N_{\mathcal{V}}} \sum_{\mathcal{V}_j \in \mathcal{N}(\mathcal{V}_i)} \delta(\mathcal{V}_i, \mathcal{V}_j), \end{aligned} \quad (6)$$

where $\mathcal{N}(\mathcal{V}_i)$ denotes the set of vertices within the one-ring neighborhood of $\mathcal{V}_i$, and the first two terms of the energy function are data fidelity terms which are defined as the negative log-likelihood of the distribution p_S and p_L of area distortion ratio r_{AD} on small and large vessel surfaces, respectively. Both the mean and standard deviation of the area distortion ratio distributions p_S and p_L are estimated by fitting a Gaussian model. The same threshold value $r_{AD} = 0.6$ is chosen to roughly categorize the feature map into two classes for the estimation (as shown in Fig. 6(b)). The third regularization term is used to penalize

discontinuities between neighboring vertices, and the regularization parameter λ is employed to balance data fidelity and boundary smoothness.

To minimize the energy, we employ the graph-cut segmentation technique [37] which has often been used to compute the global minimum for different optimization tasks [38]. Here a graph $\mathcal{G} = (\tilde{\mathcal{V}}, E)$ is constructed to obtain the graph cut between large vessel vertices and small capillary vertices. $\tilde{\mathcal{V}}$ denotes the set of vertices in $\mathcal{G}$ and is defined as $\tilde{\mathcal{V}} = \mathcal{V} \cup \{T_S, T_L\}$, which is the union of vertices in mesh $\mathcal{M}$ and two terminal nodes T_S for small capillaries and T_L for large vessels. The max-flow algorithm reported in [39] are used to compute the maximum flow from T_S to T_L . The final regions $\mathcal{D}_S$ and $\mathcal{D}_L$ are obtained as the set of vertices connected to T_S and T_L , respectively. If a vertex $\mathcal{V}_i$ is classified into the small capillary group, then we set its label $\mathcal{L}_{\mathcal{V}_i}$ as 1. Otherwise, we set the label as 0. In Fig. 6(d), we show a typical example of the graph-cut based segmentation results on 3D OCT-A vessel mesh surfaces, which presents more accurate vessel classification performance than the direct thresholding shown in Fig. 6(c).

C. Shape-Based Biomarker Extraction of Mesh Surface Areas

The smooth microvascular surfaces provide a more intuitive and accurate 3D data representation compared with the discrete volume-based representation with jagged mask boundaries. By performing shape analysis on such a high-quality surface representation, one can easily quantify important local variations based on the rich surface-based vascular geometry and topology. For instance, useful features like capillary loops, branchings or other biological patterns can be quantified as important shape-based biomarkers for further analysis. The 3D surfaces can also be simplified as a graph structure to locate critical geometric and topological changes.

In this work, we perform preliminary analysis using mesh surface areas as a feature to show the great potential of exploring shape-based biomarkers for disease studies. We also aim to show the importance of performing separate analysis on large vessels and small capillaries. To this end, each of the triangular faces is classified into the large vessel and small capillary groups according to the segmented labels $\mathcal{L}_{\mathcal{V}_j^k}$ of its three vertices $\mathcal{V}_j^k$, where $k = \{1, 2, 3\}$ and $\mathcal{V}_j^k$ is the k -th vertex of a triangle $\mathcal{T}_j$. Most of the triangles belong to large vessel group and some of the triangles in segmentation boundary have only one vertex belonging to the small capillary group. Here we give more tolerance to small capillaries to make sure that all their possible triangular faces can be taken into account. Therefore, we set the label of a triangular face to 1 if there exists at least one of its vertices with a label 1, i.e., $\sum_{k=1}^3 \mathcal{L}_{\mathcal{V}_j^k} \geq 1$. Otherwise, we set the label to 0. The mesh surface areas biomarker $\mathcal{A}_L$ and $\mathcal{A}_S$ of large vessels and small capillaries are obtained by summing $\text{Area}(\mathcal{T}_j)$ of all triangles in the two groups separately.

IV. Validation Using 3D Repeated OCT-A Scans

To validate a comprehensive 3D OCT-A vessel modeling framework is challenging due to the low possibility of annotating a 3D complex microvascular network as ground truth. Hence, we propose to evaluate the *test re-test reliability* of the surface reconstruction framework through 3D repeated OCT-A scans. We aim to see if the proposed framework could reliably replicate the similar result using any of the repeated scans of the same subject under the same parameter settings. More specifically, if the proposed shape modeling framework is able to produce high consistency and shape similarity between any two of the repeated 3D OCT-A scans, it is considered as having high *test re-test reliability*, and therefore is suitable for performing 3D OCT-A microvascular modeling and analysis. In addition, by comparing the repeated scans, typical issues such as variations of retinal vasculature, motion/projection artifacts during the OCT-A imaging process can be potentially investigated. It also provides the possibility of fusing multiple repeated scans together into a more complete 3D OCT-A microvascular representation for future analysis.

In this study, the OCT(-A) repeated scans (RS) dataset has been set up by imaging both the left and right eyes of 13 subjects via a commercial Zeiss spectral domain (SD)-OCTA. Each eye was repeatedly photographed for 10 times with an interval of 10 seconds between every two scans. Prior to examination, written informed consents were obtained from subjects in accordance to the tenets of Declaration of Helsinki. During the whole imaging process, the camera was set to automatically locate the same VOI centered on the fovea. Finally, we collected in total 260 volume images from the 13 subjects in the RS dataset for validating the repeatability of our method.

However, 10 repeated scans from the same subject are not perfectly aligned with each other due to involuntary fixational eye movements (e.g., micro saccades and drift) during imaging process, as well as imperfect processing of motion artifacts which can cause distortions of local vessel structures [40]. See Fig. 7 for an example. Such mismatches between scans of the same subject will lead to an unreliable shape similarity comparison. Hence, an OCT-A vessel registration step needs to be designed to ensure the accurate alignment of the microvascular network before validation. As OCT-A images mainly contain the microvasculature without having other significant anatomical structures like retinal layer boundaries, it is difficult to directly register the VOI of the 3D repeated OCT-A volumes together. To handle this issue, we propose to first rigidly register their corresponding OCT volumes together, and then use the obtained deformation fields to initialize the non-linear registration of the repeated volumes as shown in Fig. 7. In this way, the OCT-A images can reach a global alignment based on their rich anatomical information (e.g. retinal layer boundaries, fovea regions) in OCT. The non-local means (NLM) filter [41] is used to improve the visibility of anatomical structures in OCT images before registration. Then, important anatomical regions with clean background are obtained for registration by masking out the vitreous and choroidal areas.

The registrations are performed using the elastix package [42]. Typically, one OCT(-A) scan is chosen by an expert as a fixed image I_f and the other nine repeated scans are treated as moving images I_m . OCT-A images present sharp boundary transitions due to very high

vessel intensities compared to background. This makes it suitable to choose the mean squared image difference (MSD) as a cost function since it can take advantage of significant voxel-based intensity differences. For the rigid OCT alignment, affine transformation model is applied, while B-spline transformation model is chosen for OCT-A registration. To find the optimal transformation parameters, a fast adaptive stochastic gradient descent optimization method [43] is used to minimize the cost function. A multi-resolution strategy is also applied to reduce the computational cost and escape the local minima. Six resolutions are chosen for the affine registration on OCT images while five resolutions are chosen for the B-spline registration on OCT-A images. All OCT(-A) images are smoothed by a Gaussian filter with a standard derivation of 16 voxels in the first resolution and halved successively in the rest resolutions. 10^5 samples of an OCT(-A) image are selected at each resolution for affine registration, while 5×10^5 samples are selected to allow more local adaptations for B-spline registration. An OCT-A image voxel has the physical size of $0.012 \text{ mm} \times 0.012 \text{ mm} \times 0.002 \text{ mm}$. We hereby set the B-spline grid space as 0.16 mm for the first resolution and halved for the successive resolutions to achieve the best alignment of the local microvascular structures. The registered 3D repeated scans of the RS dataset can then be used for the validation of the proposed tools in 3D shape modeling.

To measure the repeatability of the 3D surface of registered repeated scans, we calculate the one way Hausdorff distance from each point a_i of set A to the point set B . The distance map is given by $d_H(a_i, B) = \min_{b \in B} \|a_i - b\|$, $i = 1, \dots, N_A$, where N_A is the number of points in set A . Thus, we can calculate a distance map from the 3D reference surface to any of the registered repeated 3D surfaces. We also define a similarity ratio r_S to measure the successful overlapping between any pair of 3D OCT-A mesh surfaces of the 10 registered repeated scans per subject. r_S represents the fraction of the reference mesh vertices numbers which have the distance d_H less than a voxel diagonal length $\hat{d}$ over the whole vertices numbers, and which can be written as $r_S = \frac{1}{N_A} \sum_{i=1}^{N_A} \Theta(\hat{d} - d_H(a_i, B))$, where $\Theta(\cdot)$ is a unit step function with zero for negative argument and one for positive argument, and where we have $\hat{d} = 0.0174 \text{ mm}$ for our data.

V. Experimental Results and Validation

A. Materials

In addition to the RS dataset, we have also established a clinical OCT-A dataset on diabetic retinopathy (OCTA-DR) for shape-based vessel biomarker analysis. The OCT(-A) imaging process follows the similar standard as explained in Section IV but without any repetitions. In the OCTA-DR dataset, only one eye of each patient has been selected for analysis to ensure the independence since two eyes of a single subject could be correlated with each other. Therefore, there are in total 100 OCT-A volume images from 100 subjects including 40 normal controls (NC), 20 severe non-proliferative diabetic retinopathy (NPDR) and 40 proliferative diabetic retinopathy (PDR). For each subject, we have also collected its corresponding OCT volume image for mask generation using OCT-Explorer [34].

B. Repeatability Evaluation on 3D Microvascular Surfaces

We aim to validate the effectiveness and repeatability of the proposed shape modeling pipeline using registered 3D repeated scans of the RS dataset. The well-designed preprocessing step provides the segmented microvascular network for 3D surface reconstruction. The defined distance measure d_H and similarity measure r_S are calculated on the 3D surfaces of the registered repeated scans. For each subject, we iteratively choose each of the 10 registered surfaces as a reference and calculate the evaluation metrics with each of the other 9 remained scans separately. Hence there are in total 90 comparison values for each metric in one subject. In Fig. 8(a), we show example of the registered repeated scans on one subject from the RS dataset. We can see that the surfaces of large vessels and small capillaries on the major retinal layers are reconstructed using our microvascular surface reconstruction framework. Fig. 8(b) shows the overlapping between the registered moving surfaces with the reference surfaces, from which we can see that their mesh surfaces (in yellow and red) cover each other precisely. The Hausdorff distance map shown in Fig. 8(c) gives the average measure of 0.0071 ± 0.0140 mm. We can observe that most of the structures, in particular large vessels are accurately overlapped with distances smaller than a voxel diagonal length $\hat{d} = 0.0174$ mm.

The global performance on the RS dataset achieved by our method is provided in Table I using the mean measurements of the left eyes and right eyes separately. The proposed framework can produce vessel surfaces with high repeatability under a proper threshold range $T_{\mathcal{P}}$ of the OOF-based vessel map. We can see that extremely small surface distances (from 0.0050 mm to 0.0057 mm) and high similarities (from 0.9315 to 0.9475) are easily obtained under several different threshold values. Since the OCT-A microvascular segmentation is affected by false positives from background noise/artifacts, a relatively lower threshold value can preserve more true positives but may result in more false positives. The relation between vascular preservation and non-vascular suppression needs to be balanced to improve the accuracy of the segmented OCT-A microvascular network. Thus, we choose a relatively higher threshold value $T_{\mathcal{P}} = 0.14$ in order to reduce more false detections and meanwhile maintain high similarities of 0.9315 and 0.9324. The high similarity measures obtained from the evaluation of 260 3D OCT-A images shows high effectiveness and strong repeatability of our method. In Fig. 8(c), it is also worthwhile to note that there are a few capillary variations between repeated scans of a same subject. This means that one tiny structure can appear in one volume image but missing from another. Such small capillary variations in repeated scans may reflect that local vessel visibility is affected by the blood flow changes during the imaging process. It indicates that more complete microvascular modeling can be achieved by fusing useful local vessel variations from registered repeated scans.

C. Comparison with 2D OCT-A Segmentation Methods

Currently, most of the retinal microvascular segmentation tasks have been accomplished using 2D techniques on *en face* projections, while the 3D segmentation performance is still hard to validate due to the lack of ground truth. To further verify the reliability of the proposed 3D microvascular segmentation approach, we set up a consistency comparison

between the 2D projections of our 3D method and the 2D segmentations of the commonly used 2D techniques, i.e. the left-invariant derivatives in orientation scores (LIDOS) [19], 2D optimally oriented flux (OOF) filters [24] and 2D vesselness filters [44]. Those methods are applied to enhance and segment the 2D *en face* projections of the 3D OCT-A images in the OCTA-DR dataset. For fair comparison, the inputs of those 2D methods are also preprocessed using the same curvelet denoising procedure as in our pipeline. Afterwards, we compare the segmented vessel overlaps between those approaches and the 2D projections of our 3D processed OCT-A volumes. In Fig. 9, we see a typical example showing that the obtained 2D projection (in Fig. 9(a)) by our pipeline is able to produce high vessel visibility on both large vessels and small capillaries. It also shows better capillary preservation compared with the other 2D methods. Among the three 2D approaches, the LIDOS [19] has been reported as the best one for performing vessel segmentation tasks. In Table II, quantitative comparisons using the Dice similarity coefficient (DSC) indicate that our 3D segmentation pipeline achieves the highest segmentation overlaps of 0.8587, 0.8520 and 0.8434 with the 2D LIDOS on normal, severe NPDR and PDR groups. Similar consistency can also be observed from the comparison with 2D OOF method. In Fig. 9(d), the 2D vesselness filters produce more disconnected capillaries compared with the other techniques. Thus, it shows less overlap with the projections of the 3D pipeline. Both the qualitative and quantitative evaluations show that our approach is able to produce reliable segmentations for the subsequent shape modeling and analysis.

D. Graph-Cut Based Microvascular Classification Results

In Section III, we designed the graph-cut based segmentation approach on OCT-A vessel meshes to categorize large vessels and small capillaries separately. This allows us to perform more specific shape analysis on small capillaries to avoid the effects of tailing artifacts from large vessels. In Fig. 10, we can see three classification examples on images from the normal, severe NPDR and PDR groups separately. We can see that the tailing artifacts cause thickening effects on large vessel surfaces in z -direction. As a result, the triangular faces of large vessels produce less area distortions than small capillaries after applying the LB eigen-projection technique. The color map shown in Fig. 10(b) provides the area ratio feature projection on images of different DR stages. We can observe that consistent distributions with area ratio roughly above 0.6 on small capillaries and below 0.6 on large vessels have been achieved via the LB eigen-projection on all three subjects. This indicates the strong potential of integrating the area ratio feature into the graph-cut vessel classification framework. To obtain a representative area ratio map for each data, we design an automatic way to select the number of eigen-functions L for OCT-A vessel meshes with different amount of vertices $\mathcal{N}_{\mathcal{V}}$. In our case, we set $L = \lceil \mathcal{N}_{\mathcal{V}} / 300 \rceil$ to achieve high-quality LB eigen-projections. In Fig. 10(c), the graph-cut based classification results are given to show the successful categorization of microvasculature. All the large vessels and small capillaries are precisely classified into two different groups based on the well-established vessel area ratio feature on surfaces. We can observe that almost all the large vessels with tailing artifacts are extracted and marked as red color in Fig. 10(c). Those vessels are mainly located at the vessel trunks and the first level branches. The remained small capillaries, therefore, can be specifically investigated using shape analysis for further disease studies.

E. Statistical Analysis of Shape-Based Biomarker for DR

The 3D surface-based data representation of retinal microvasculature provides ophthalmologists with an intuitive way for observing important geometric and topological changes that is difficult to achieve based on volume data. For example, tailing artifacts can be better investigated using shape analysis on vessel surfaces, but are difficult to be analyzed using only intensity information on volume data. Based on the categorized 3D vessel meshes, we can easily extract shape-based features to show the great potential of being used as important quantitative biomarkers for DR analysis. To validate that, in Section III-C we extract the shape-based mesh surface areas to show the possibility of examining differences between different DR groups. In Fig. 11, we show the statistical analysis results on the clinical OCTA-DR dataset including 100 subjects of normal, severe NPDR and PDR cases. To evaluate the significance on different vessel structures, the mesh surface areas of large, small and all vessels on each volume image are respectively calculated based on the classified triangular faces.

Statistical analysis is performed using Wilcoxon rank sum test on every two independent groups. In Fig. 11(a)-(b), we can observe that the shape-based mesh area biomarker on small capillaries achieves the best performance (with p values < 0.001) in distinguishing different DR stages, while on large vessels it only presents significance between normal and PDR groups. There are no significant differences observed between normal and severe NPDR groups, and between severe NPDR and PDR groups from the statistical analysis performed on large vessels. Nevertheless, statistical significance (with p values < 0.05) of the three different groups can be obtained when adding the mesh area of small capillaries and large vessels as shown in Fig. 11(c). We can clearly see that small capillaries play the most important role on the detection of DR group differences. This is consistent with previous findings that fine capillaries are important structures to support DR analysis. The tailing artifacts on large vessels could be the main cause for getting weak statistical differences. The analysis on vessel surfaces also reflect the characteristics on volume data. It shows the importance of analyzing small capillaries independently and the necessity of excluding tailing artifacts for further studies of microvascular disorders using shape modeling and analysis.

F. Statistical Comparisons of 2D and 3D Biomarkers for DR

To show the potential benefits of exploring the 3D OCT-A microvascular biomarkers, we perform preliminary comparisons between 2D and 3D vessel biomarkers as shown in Fig. 11 and Fig. 12. The commonly used 2D vessel area density (VAD) and vessel skeleton density (VSD) [4] are both calculated from the microvascular segmentation results of 2D *en face* projections on the same subjects from the OCTA-DR dataset. For 2D biomarkers, we can observe (in Fig. 12) significant statistical differences between normal and the other two groups with $p < 0.001$, while there are no significant differences between the severe NPDR and PDR groups on both 2D VAD and VSD biomarkers with $p = 0.772$ and $p = 0.495$, respectively. These findings are consistent with the previous statistical analysis performed on 2D *en face* vessel biomarkers for DR [4]. However, we do find significances (with $p < 0.001$ and $p < 0.05$) respectively in the analysis of small capillaries and all vessels on the 3D vessel surface area biomarker for differentiating the severe NPDR and PDR groups, as shown in

Fig. 11(a) and (c). Due to the overlay of vessels in the 2D *en face* representation of 3D microvascular network, the subtle 3D microvascular changes can be obscured in 2D projections. It could decrease the sensitivity of the 2D VAD and VSD measurements for distinguishing severe NPDR and PDR stages. Our results may indicate surface-based biomarkers are able to provide valuable 3D microvascular information which is obscured in 2D analysis. The statistical comparisons between 2D and 3D microvascular biomarkers thus demonstrate the potential of further exploring rich 3D geometric and topological features for retinal diseases diagnosis.

VI. Conclusion

In this work, we have developed a 3D shape modeling and analysis framework for studying retinal microvasculature based on OCT-A. This is for the first time that a comprehensive surface-based framework has been applied to analyze 3D OCT-A microvasculature. Two well-established clinical datasets including in total 360 volume images have been extensively used for repeatability validation and disease analysis. The high evaluation performance on the RS dataset shows the robustness of our 3D shape modeling framework on processing OCT-A microvasculature. Shape analysis has been performed on microvascular surfaces to categorize large vessels and small capillaries for independent evaluation. It shows the great potential of exploring surface-based analysis for further microvascular study. Preliminary investigation using vessel surface areas shows the promise of extracting valuable shape-based vessel biomarkers for studying retinal diseases. The proposed framework thus provides a novel and reliable tool for modeling and analyzing 3D OCT-A data.

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Fig. 1.

An overview of the proposed OCT-A shape modeling and analysis framework.

Fig. 2.

An example of obtaining the final 3D OCT-A vessel segmentation via curvelet denoising, OOF enhancement and well-composedness preservation.

Fig. 3. Visualization of (a) the 3D OCT volume, (b) different retinal slabs, and the 2D *en face* projections of the (c) superficial and (d) deep retinal layer.

Fig. 4.
3D OCT-A triangular mesh surfaces with geometric outlier removal.

Fig. 5.
Large vessel thickening caused by tailing artifact.

Fig. 6.
Example of graph-cut based vessel surface classification using the area ratio map.

Fig. 7. OCT-A registration based on OCT rigid transformation followed by a non-linear OCT-A registration to refine the local matching.

Fig. 8. Similarity measurement on repeated scans. (a) gives the 3D mesh surfaces of one subject. (b) shows the overlapping between the registered moving (in yellow color) and fixed (in red color) mesh surfaces. (c) provides their Hausdorff distance map.

Fig. 9.

Comparison with different 2D vessel segmentation techniques. Row 1: the enhanced vessel map, and Row 2: the binarized vessel map.

Fig. 10.

Examples of the LB eigen-projection and microvasculature segmentation on different groups. (a) The 3D vessel mesh surfaces, (b) the vessel area distortion ratio map, and (c) the classification results of large vessels (in red color) and small capillaries (in yellow color) are shown in different columns.

Fig. 11.

Statistical analysis of the mesh surface area biomarker for different stages of DR based on large vessels, small capillaries and all vessels separately.

Fig. 12. Statistical analysis of 2D vessel area density and vessel skeleton density for different stages of DR.

TABLE I

Similarity measures between 3D mesh surfaces of 10 repeated OCTA scans under different threshold values

$T_{\mathcal{P}}$	0.10	0.11	0.12	0.13	0.14
$d_H^{\mu}(Left)$	0.0050	0.0052	0.0054	0.0055	0.0056
$r_S^{\mu}(Left)$	0.9475	0.9405	0.9349	0.9319	0.9315
$d_H^{\mu}(Right)$	0.0053	0.0056	0.0057	0.0057	0.0056
$r_S^{\mu}(Right)$	0.9417	0.9356	0.9327	0.9316	0.9324

TABLE II

Consistency comparison with 2D segmentation techniques

<i>Methods</i>	Normal	Severe NPDR	PDR
3D Pipeline vs 2D Vesselness [44]	0.7992	0.7901	0.7888
3D Pipeline vs 2D OOF [24]	0.8379	0.8404	0.8317
3D Pipeline vs 2D LIDOS [19]	0.8587	0.8520	0.8434