Abstraction
Wide-field fluorescein angiography (FA) images are commonly used in ophthalmology to assess longitudinal changes in retinal vasculature, specifically, non-perfusion. Current practice relies on manual qualitative comparisons between images taken at successive clinic visits, a few months apart. Objective quantitative assessments, although desirable for evaluating disease progression and treatment, are impractical to perform manually and challenging for image analysis because of the changes in the capture viewpoints and temporal imaging variations seen as the FA dye injection perfuses the retina. We propose a methodology for quantifying retinal non-perfusion by automated analysis of the FA images captured during successive clinical visits. Blood vessels are first detected in the image from each visit. The vascular networks in FA images are then precisely registered to obtain a co-aligned pair via parametric chamfer matching under polynomial transformation, a process that explicitly allows for increase or decrease in perfusion. Changes in perfusion are then quantified by identifying the common and distinct regions in co-aligned image pairs. The proposed framework is tested on FA images that are manually annotated by an ophthalmologist to provide ground truth binary vessel masks and to identify vasculature changes. Results indicate that the proposed method provides assessments of vasculature changes that are in good agreement with the ophthalmologist-provided annotations.

Index Terms— wide-field fluorescein angiography, vessel detection, image registration, expectation maximization (EM)

1. INTRODUCTION

Common systemic diseases, such as diabetes, hypertension, and atherosclerosis affect blood vessels throughout the body [1]. Retinal non-perfusion (RNP), or ischemia, which is a lack of blood flow to the retina, directly results in the most severe blinding complications of systemic diseases in the eye, including proliferative diabetic retinopathy, tractional retinal detachments, vitreous hemorrhage, and neovascular glaucoma. The impact of RNP on the vascular system can be visualized in using wide-field fluorescein angiography (FA), a process that involves injecting fluorescein dye intravenously and taking images that capture the fluorescence of the dye passing through the retinal blood vessels using a fundus camera with suitable optical filters [2]. Figure 1 shows two samples FA images taken for one patient over time. Compared to alternatives such as color fundus images, FA image has the advantage that they provide wide field of view (FOV). Typically, color fundus images capture only a 30° to 60° FOV, whereas wide-field FA permits up to 200° FOV. The wide FOV allows visualization of the retinal vasculature. As shown in Fig. 1, peripheral vessels are captured with sufficient details. The wide FOV allows imaging of the peripheral region of retina, which makes it possible to measure the relative changes of peripheral retinal vessels.

The ability to quantify RNP is important to: 1) develop a reproducible method to compare changes in RNP over time in different diseases, 2) evaluate the impact of systemic or local treatments on vessel changes over time, and 3) better understand the relationship between RNP and other ocular changes such as macular edema and visual acuity. In current clinical practice, ophthalmologists manually examine retinal images to assess RNP and changes in blood vessels occurring over time. Quantitative manual assessments in clinical setting are impractical because the processes are extremely time-consuming. Automated methods for measuring retinal vascular changes are highly desirable for providing quantitative assessments that correlate with disease/treatment progression and assist physicians in diagnosis and treatment.

Currently there are no widely accepted automated techniques for FA image analysis that quantify blood vessel changes and RNP in the retina. A preliminary approach was proposed in [2], which attempts to quantify the dark regions corresponding to background and non-perfused vessels. Given the relatively large regions without blood vessels, the method has limited sensitivity and does not allow for physician validation because it does not explicitly identify the non-perfused vessels. Direct quantitative measurement of vessel changes is challenging for several reasons. First, because the capture viewpoints differ between different visits, FA images need to be accurately registered before any comparison can be made. The registration, however, is not entirely trivial because of the changes in the vessels (which we are trying to quantify) and variations in time duration elapsed from the dye injection to the instant when the images are captured, which results in different vasculature appearances as the injected dye propagates in the retina.

In this paper, we propose a novel methodology to quantitatively measure the vasculature changes, specifically, RNP, using wide-field FA
images captured at successive clinical visits. To overcome the aforementioned challenges, we propose a novel registration and change detection approach. The images are first independently analyzed to detect blood vessels. A pair of vessel images are then precisely registered using parametric chamfer alignment under polynomial transformation. The conventional chamfer alignment procedure is adapted to our specific problem setting to allow for changes in blood vessels between the two images. Specifically, we exploit the inherent asymmetry in the chamfer metric between the reference and target images, wherein for each point in the target binary image, the closest point in the reference binary image is considered for defining the registration error under the parametric transformation. The process is further enhanced by using a modified chamfer metric that also weights the estimated registration error for each vessel pixel in the target according to the probability that a corresponding pixel exists in the reference. The probabilities are estimated via an expectation-maximization (EM) procedure. In combination, the asymmetry and the EM based probabilistic formulation of the chamfer metric allow for mismatch between the two images arising due to both changes in vasculature and missed vessel detections.

The individual ingredients of vessel detectoin and registration that we use in our methodology have considerable existing related prior work. Vessel detection has been extensively researched for color fundus images [14–19], although there is relatively little work for FA imagery [17]. Existing retinal image registration methods rely on determining correspondences between images. For instance, in [14], the method for the multimodal fundus images registration is proposed using the locations of vascular bifurcations. Edge-based features [15] also have been exploited. [16] proposed a method to register wide-field FA images based on bifurcations and elongated elements. These methods are more suited for the problem of registering the multiple images taken during a single clinic visit where changes occur as the dye perfuses but are small from image to image and there is no fundamental change in the vasculature. The methods face significant challenges in aligning images from different clinical visits due to the missing correspondence and bifurcation points in one image relative to the other.

The paper is organized as follows. We describe the proposed method in Section 2 and present the experimental results in Section 3. Section 4 summarizes the concluding remarks.

2. PROPOSED METHOD

The proposed method addresses the problem of quantitatively and directly measuring retinal blood vessels to assess the clinically significant changes occurring in retinal vasculature over time. The pipeline of the proposed method is depicted in Fig. 2. It takes as input a pair of FA images for a patient captured at successive visits. Blood vessels are first extracted in the image from each visit using vessel detection method [17], as illustrated by the images labeled as “detected vessels” in Fig. 2. Using parametric chamfer alignment [18, 19], the binary vessel images are precisely registered to obtain a co-aligned pair. The chamfer alignment is performed using an EM framework, which is robust to outliers that correspond to vessels presented only in one temporal instance due to vasculature changes. The co-aligned pair identifies both common and distinct regions of vasculature and allows quantitative assessment of the changes in retinal non-perfusion.

![](https://via.placeholder.com/150)

**Fig. 2.** Proposed methodology for measuring retinal vasculature changes using FA images.

### 2.1. Vessel Detection

As shown in Fig. 1, the longitudinal FA images normally differ in the capture viewpoints and in the time elapsed from the injection of the dye to the capture of the images, introducing variations in the images that do not allow for direct quantitative comparison. Therefore, the first step of the proposed method is to detect vessels from two input FA images.

The retinal blood vessels inherently exhibit variations in different orientations and changes in scales between major and minor branches. To take into account these characteristics of vessel structures, we adopt a vessel detection method [17] that uses a set of oriented modified top-hat morphological filters with multi-scale analysis. Decomposing the original FA image into multiple scales, the vessels at each scale are detected independently and then fused together to achieve the final binary vessel map. Modified morphological top-hat operators with linear structuring elements with different orientations are used to extract bright and rectilinear structures with matching orientation, which represent the shape of blood vessels in the image. Figure 3 shows the results of vessel detection for the images in Fig 1.

![](https://via.placeholder.com/150)

**Fig. 3.** Sample results of detected vessels for images shown in Fig. 1.

### 2.2. Retinal Image Registration

We propose to register a pair of binary vessel images obtained from Sec. 2.1 using parametric chamfer matching [18, 19]. We denote one binary vessel image as reference \( I_r \) and the other as target \( I_t \). Let \( P = \{ p_i \}_{i=1}^{N_p} \) and \( Q = \{ q_j \}_{j=1}^{N_q} \) be two sets of points of vessel pixels in the reference and the target images, respectively, where \( p_i = (x_i, y_i) \) and \( q_j = (u_j, v_j) \). We apply the second-order polynomial transformation \( T_{p_t} \) to map target points to the reference
points. The transformation of target points, \( T_\beta(q_j) \), is modeled as

\[
T_\beta(q_j) = \left[ \beta_1 \beta_7 \right] + \left[ \beta_2 \beta_3 \beta_4 \beta_8 \ldots \right], \tag{7}
\]

where \( N_r, N_g, \) and \( N_b \) are the number of pixels of common region, added perfusion, and lost perfusion, respectively.

The chamfer distance, \( d_j(\beta) \), between reference points \( P \) and each transformed target points \( T_\beta(q_j) \) is defined as the distance between \( T_\beta(q_j) \) and its nearest point from \( P \)

\[
d_j(\beta) = \min_i \|p_i - T_\beta(q_j)\|^2. \tag{2}
\]

The optimal registration between images \( I_r \) and \( I_t \) is achieved by determining the transformation parameters that minimizes the error metric

\[
\hat{\beta} = \arg\min_\beta \frac{1}{N_t} \sum_{j=1}^{N_t} d_j(\beta), \tag{3}
\]

where \( N_t \) is the number of points in the target image \( I_t \).

Observe that chamfer matching in (3) is asymmetric: because the error is aggregated only over points in the target image, points in the reference image with no corresponding points in the target image do not contribute to the error metric. Because the changes we are interested in are manifested primarily as increases or decreases in perfusion, we exploit this asymmetry by considering both possible choices for the reference and target image allocations and choosing the one with the smaller mean chamfer distance\(^2\). While this is beneficial, the formulation in (3) still faces a challenge from differences of interest while ignoring minor inaccuracies in registration and variations in estimated vasculature thickness caused by other imaging parameters, such as time duration elapsed from the dye injection to the instant when the images are captured. As shown in Fig. 4 (b), regions of vasculature shown in red are identified as common, in blue as those with lost perfusion, and in green as those with added perfusion.

2.3. Change Quantification

Given the estimated parameters \( \hat{\beta} \), we apply the second-order polynomial transformation to the target image \( I_t \). Changes in retinal vessels can be quantified and visualized from the co-aligned pair.

Figure 4 shows an example illustrating the process of comparing and quantifying retinal blood vessels differences from the co-aligned pair. Fig. 4 (a) illustrates the results of alignment, obtained in Sec. 2.2, by superimposing the images as red (earlier in time) and green channels (later in time) so that common locations are identified as yellow. The co-aligned images are further processed to quantify differences of interest while ignoring minor inaccuracies in registration and variations in estimated vasculature thickness caused by other imaging parameters. Quantitatively, the percentage increase of blood vessel perfusion \( K_t \) and percentage decrease of perfusion \( K_d \) can be calculated as

\[
K_t = \frac{N_t}{N_r}, \quad K_d = \frac{N_t}{N_e}, \tag{7}
\]

where \( N_r, N_e, \) and \( N_t \) are the number of pixels of common region, added perfusion, and lost perfusion, respectively.

\[\text{Fig. 4. Example illustrating automated comparision and quantification of blood vasculature differences.}\]

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3. EXPERIMENTAL VALIDATION

We identify two patients who have a large amount of RNP and collect FA images to test the performance of the proposed method. The images are captured by an Optos California camera [23] at 200° FOV. Each image is manually annotated by an ophthalmologist to provide ground truth binary vessel masks using VAMPIRE annotation tools [10]. Only two images are used in the assessment because manual annotation is rather time intensive, annotation tools notwithstanding. For the first patient (P1), regions around fovea are identified corresponding to changes in vessel perfusion, and for the second patient (P2), changes occur in peripheral regions. Figure 5 shows the fovea regions of longitudinal FA images for P1 and corresponding manually annotated binary vessel maps.

![Sample ground truth vessel images](image)

**Fig. 5.** Sample ground truth vessel images. (a) and (c) show the fovea regions in the FA images where vessel changes are identified by an ophthalmologist. The images in (a) and (c) are captured at initial visit and 4 months later, respectively. (b) and (d) are manually labeled vessel maps for (a) and (c), respectively.

3.1. Quantitative And Qualitative Comparison

In our experiments, we apply the proposed method to identify and measure the changes in RNP over time and compare with ground truth in terms of the percentage increase of vessel perfusion $K_i$, percentage decrease of perfusion $K_d$, as well as the number of pixels of common region $N_c$, increased perfusion $N_g$, and lost perfusion $N_d$.

We choose the FA image of the initial visit as reference and the one of later visit as target. Table 1 lists the quantitative comparison in terms of the 5 aforementioned metrics for two patients. For the first patient (P1), the percentage increases $K_i$ and decrease $K_d$ are close to the ground truth values. The proposed method estimates 10.4% and 35.8% of increased and decreased perfusion in blood vessels, whereas ophthalmologist-provided estimates are 8.1% and 35.5%, respectively. A visual comparison for the first patient is illustration in Fig. 6 (a) and (b), which show ground truth and results of the proposed method, respectively. Regions of vasculature shown in red are identified as common, in blue as those with lost perfusion, and in green as those with increased perfusion. It can be seen that most changes are correctly identified, with the exception of some fine vessels around the fovea.

![Visual comparison of vessel change detection](image)

**Fig. 6.** Visual comparison of vessel change detection. (a) and (c) show the ground truth for P1 and P2, respectively, and (b) and (d) show the results of proposed method for corresponding patients. The vessels in red, green, and blue are identified as common, lost perfusion, and increased perfusion, respectively.

<table>
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<th>$K_i$</th>
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<th>$N_c$</th>
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**Table 1.** Quantitative results of vessel changes measurement. GT stands for ground truth.

For the second patient (P2), peripheral regions are identified as changes in vessel. Figure 6 (c) and (d) show the ground truth and the results of proposed method for this patient, respectively. We can see that both decreased and increased perfusion can be identified: most decreased perfusion happens in the right side in Fig. 6 (d) whereas increased perfusion are identified in the bottom left corner in Fig. 6 (d). The results of visual examination are accordance with that of quantitative comparison.

4. CONCLUSION

We propose a method for direct quantification of longitudinal changes in retinal vessel from wide-field FA images comprising three steps: vessel detection, retinal image registration, and change quantification. The key contribution is a novel second-order polynomial transformation based parametric chamfer alignment procedure. Specifically, by using a probabilistic formulation and exploiting inherent asymmetry, the proposed chamfer alignment approach allows precise registration of FA images taken from different viewpoints and several months apart despite changes in the vascular network and variation in dye perfusion. The precision registration enables accurate automated assessment of changes. Both qualitative and quantitative results indicate that the proposed method provides accurate assessments of retinal vasculature changes that are in agreement with ophthalmologist-provided annotations.

5. ACKNOWLEDGMENT

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6. REFERENCES


