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A Novel Automated Retinal Image Fusion using Adaptive Exploratory Algorithm and Mutual-Pixel-Count Maximization

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Abstract— **A novel automated approach of the multi-modality retinal image registration and fusion has been developed. The new algorithm, which is reliable, robust, and time-efficient, has an automatic adaptation from frame to frame with few tunable threshold parameters. The registration is based on retinal vasculature extraction using Canny Edge Detector, and control point identification at the vessel bifurcations using adaptive exploratory algorithm. Shape similarity criteria are employed to match the control points. MPC maximization based optimization has been developed to adjust the control points at the sub-pixel level. MPC, which is initially introduced by this study into the biomedical image fusion area, is the new measurement criteria for fusion accuracy. A global maxima equivalent result is achieved by calculating MPC local maxima with an efficient computation cost. The comparative study has shown the advantage of the new approach in terms of novelty, efficiency, and accuracy.**

Index Terms — Area-based fusion, feature-based registration, biomedical image registration and fusion, adaptive exploratory algorithm, mutual-pixel-count, retinal vasculature extraction.

I. Introduction

An urgent requirement of clinical practice for the patients' retinopathy studies has, more than ever before, necessitated the development of the computer-based multi-modality retinal image fusion techniques. Retinopathy, which is usually due to damage to the blood vessels next to the retina, covers various diseases and disorders of the retina. It is critical to treat eye diseases or injuries that affect the retina as early as possible. Otherwise, it is possible to get the blurred vision, or even get completely blindness. In practical clinical applications, the comparison of angiogram grayscale images with fundus color images is often required in order to identify dynamic aspects of the circulation and evaluate various retinal vascular disorders. This study provides a convenient way for the early detection of various retinal abnormalities.

Area-based and feature-based approaches are widely employed for medical image registration and fusion. Mutual Information (MI) is the traditional fusion accuracy measurement in the area-based technique [1]. This study borrowed Mutual Information idea and simplified it to Mutual-Pixel-Count (MPC). MPC measures the overlap pixels of the retinal vasculature. If the images are perfectly geometrically aligned, MPC represents the maximal pixel correspondence. Feature-based method has shown to receiving higher successful rate at the multi-modality fusion scenario than the area-based method [2]. The feature means the salient structures, such as the central line of vessels and the vessel bifurcation points in the retinal network. This approach belongs to the combined category. In the feature-based registration, a new contribution is made by using adaptive exploratory algorithm to identify the global direction change pixel at the Canny edges. By locating control points at the global direction change pixel, local direction changes are efficiently avoided. The second contribution is the area-based optimization fusion. Mutual-Pixel-Count (MPC) is a new and unique concept in the biomedical image fusion area, as the fusion accuracy measurement.

II. Acquisition Process of Retinal Image

Retinal images presented in this paper were taken by a Topcon TRC-50EX fundus camera. The subjects of the retinal images were Cynomolgus monkeys of 4 to 4.5 years of age and 2.5 to 3 kg body weight with normal eyes [3]. The experimental monkey was anesthetized with the intramuscular ketamine (7-10mg/kg), xylazine(0.6-1 mg/kg), and intravenous pentobarbital (25-30 mg/kg). Administration of the anesthetics was repeated alternately every 30 minutes as required to maintain the animal in deep, stage IV anesthesia [3]. Establishing animal models is an essential prerequisite of the development of new therapeutic interventions on human diseases. Monkey species provide appropriate preclinical models that can closely reflect human's physical and physiological

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characteristics because of their very close phylogenetic relationship to human beings [4].

III. Feature-Based Registration and Area-Based Fusion of Retinal Images

A. Retinal Vasculature Extraction

Prior to fusion, image pairs need to be registered pixel-by-pixel through a mapping function T. Firstly, the new approach binarizes the reference angiogram grayscale image and the input fundus camera image. A global adaptive threshold developed by Otsu [6][7] is employed to convert the gray level colors to only black and white (Fig. 1). The output binary image has values of 0 for all pixels with the original luminance/intensity less than Otsu's threshold and 1 for all other pixels. Otsu's threshold is a normalized intensity value that lies in the range [0, 1]. The color image needs to be converted into 8-bit gray scale prior to converted into the binary image.

Chain code criteria are the well-known boundary representation technique [2]. A digital curve can be represented by an integer sequence based on the position of the current edge pixel to their eight neighbors at 2D spatial domain: $N_i \in \{1, 2, 3, 4, 5, 6, 7, 8\}$

where,

1 – South, corresponding to an angle of 270 °;
2 – North, corresponding to an angle of 90 °
3 – East, corresponding to an angle of 0 °
4 – West, corresponding to an angle of 180 °
5 – Southeast, corresponding to an angle of 315 °
6 – Northwest, corresponding to an angle of 135 °
7 – Southwest, corresponding to an angle of 225 °
8 – Northeast, corresponding to an angle of 45 °

Canny Edge Detector [8] [9] is employed to extract the vasculature (Fig. 2) from the binary image. Canny's method detects edges at the zero-crossings of the second directional derivative of the image. It performs zero-crossings of

$$\frac{d^2(G \times I)}{dn^2} = \frac{d((\frac{dG}{dn}) \times I)}{dn} \qquad (1)$$

where, n is the direction of the gradient of the image; G is the edge signal; I is the image intensity. The zero-crossings of Canny's method correspond to the first directional-derivative's maxima and minima in the direction of the gradient. Each pixel's edge gradient is computed and compared with the gradients of its neighbors along the gradient direction.

B. Control Points Selection Using Adaptive Exploratory Algorithm

Control points are identified at the vessel bifurcations on the Canny edge, which represents the strong feature of the retinal vasculature (Fig. 3). The vessel tracking is efficiently performed in the adaptive exploratory algorithm without traveling at every pixel. The algorithm traces the vasculature by locating an initial point and exploiting the local neighbors [5]. The control points will be identified at the global direction-changing pixels. ROLLBACK thresh is used to determine whether or not a direction change is local. When rollback is triggered, the direction change is identified as a local change, and thus the direction-changing pixel should not be considered as a vessel bifurcation. Shape similarity criteria are used to match the control points and minimum distance criteria is used to find the best match.

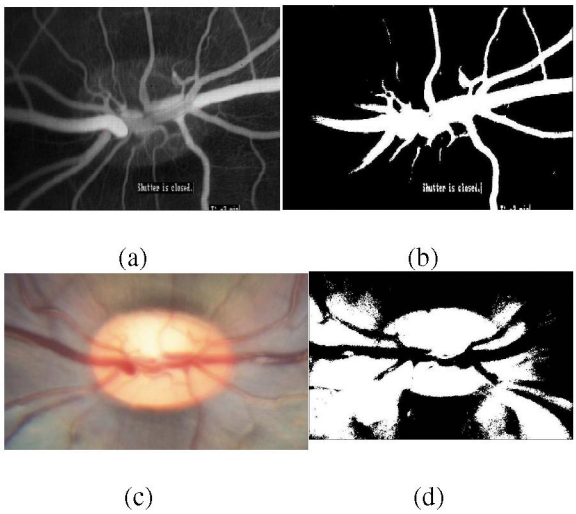


Fig.1: Original images and the corresponding binary image using Otsu's threshold. (a) and (b): angiogram grayscale image and its binary image; (c) and (d): fundus color image and its binary image.

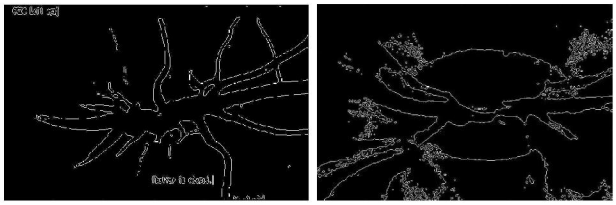


Fig. 2: Original Image Contour Extractions Using Canny Edge Detector (Because the Fundus image's B/W image is originally converted from a color image, the vessels are not as clear as those of IVFA images'.)

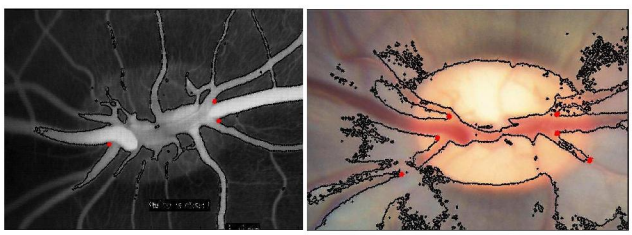


Fig. 3: Angiogram and Fundus images' control point selection

C. Optimization Fusion Algorithm Based on Mutual Pixel Count Maximization

A good guess of the control points improves the probability of convergence and the quality of the fused image. An optimization is needed to adjust the good-guess control points in order to make them accurate for achieving an optimal result. This study has developed a new automated optimization iteration algorithm based on Mutual-Pixel-Count maximization. A refinement of the solution is obtained at the end of each loop, and finally a satisfying fused image is generated at the end of the iteration (Fig. 4).

MPC measures the retinal vasculature overlap for corresponding pixels in both images. When a vasculature pixel's transformed coordinates on the input image correspond to a vasculature pixel's coordinates on the reference image, the MPC is incremented by 1. MPC is assumed to be maximal if the image pair is geometrically aligned by the transformation T. To solve the optimization problem, a global optimization schema is desirable by achieving global maxima, but with the tradeoff on expensive computation cost. In practice, a local optimization schema is usually employed to reduce the computation cost. However, local optimization can be attracted to local maxima [10]. This study developed a new local maxima scheme and achieved a global maxima equivalent result with an efficient computation cost. The entire retinal vasculature is split into three regions, i.e. west region, middle region (optic nerve head), and east region. Only two regions among three are selected for MPC calculation. The east region and the west region are the preferred ones. The middle region is the backup in case that either of the former regions is not qualified. By only calculating partial retinal vasculature, an optimal result is obtained by achieving a maximal MPC that is very close to the global maxima.

The optimization algorithm finds the optimal similarity measure by refining transformation parameters in an ordered way. During the iteration, control points of the reference image are fixed and those of the input image are subject to adjustment. Coordinates of the control points are moved to one direction till MPC stops increasing (Fig. 5). A maximum allowable loop number L is set to avoid redundant computation for mismatched control points, which leads to fusion failure. Convergence criteria are used to determine when the iteration is finished. Adjustment of the coordinates is iteratively implemented until either of the following convergence criteria met: (1). Predefined maximum number of loops has been reached. (2). Updated Mutual Pixel Count ∇MPC is smaller than ε, i.e. $|MPCn_{+1} - MPC_n| < \varepsilon$. ε is a very small non-negative threshold value.

D. 2D Affine Transformation Model

2D affine transformation model is applied to register the fundus color image into the angiogram grayscale image. Affine model is able to measure the lost information such as skew, translation, rotation, shearing and scaling that maps finite points to finite points and parallel lines to parallel lines. Once three pairs control points' coordinates are available, the procedure is able to apply them to the 2D affine model and solve the Gaussian matrix to get the parameters $P \in \{a_1, a_2, a_3, a_4, b_1, b_2\}$.

$$\begin{bmatrix} U \\ V \\ 1 \end{bmatrix} = \begin{bmatrix} a_1 & a_2 & b_1 \\ a_3 & a_4 & b_2 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \\ 1 \end{bmatrix} \tag{2}$$

$$U(x, y) = a_1x + a_2y + b_1 \tag{3}$$

$$V(x, y) = a_3x + a_4y + b_2 \tag{4}$$

$$\begin{bmatrix} u_1 \\ v_1 \\ u_2 \\ v_2 \\ u_3 \\ v_3 \end{bmatrix} = \begin{bmatrix} x_1 & y_1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & x_1 & y_1 & 1 \\ x_2 & y_2 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & x_2 & y_2 & 1 \\ x_3 & y_3 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & x_3 & y_3 & 1 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ b_1 \\ a_3 \\ a_4 \\ b_2 \end{bmatrix} \tag{5}$$

IV. Results Comparison with Other Existing Fusion Approaches

When comparing the new approach with other existing image fusion methods, the new approach has advantages in terms of accuracy, efficiency, and automation.

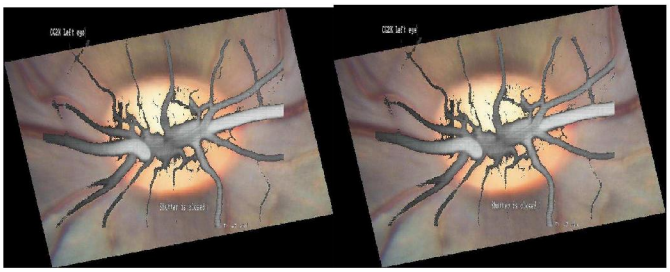
In manual approach, the ophthalmologist identifies control points at vessel bifurcations, which are common to both images. The disadvantage of human-interactive approach includes, but not limited to inaccuracy in the placement of control points, inconsistency of the fusion results, and significantly increased interaction time during manual adjustment of the control points. The fusion result from the automated approach has an apparently higher quality than the one created by manual approach.

The average time of the manual fusion approach is 35 minutes, including initial control point selection, manual adjustment of control points' coordinates, and evaluation of the fusion result after each adjustment. B. Ma proposed three computer-aided strategies in [10]. Among them, stratified sampling with centroid refinements strategy achieved shortest average running time of 11 minutes for satisfactory fusion results. G. Matsopoulos and N. Mouravliansky proposed an automatic retinal image fusion scheme using global optimization techniques in [11]. They reported an average execution time of 4.5 minutes. With less than 1 minute running time, the new algorithm therefore, has significant advantage when compared with these five approaches (Table I).

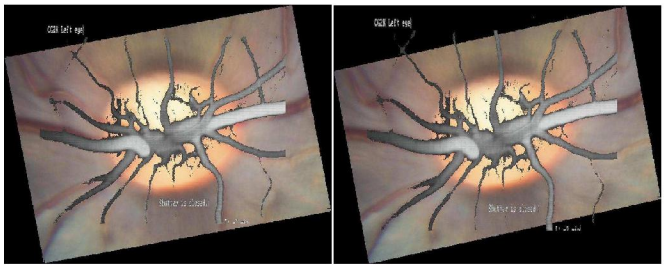
TABLE I
RUNNING TIME COMPARISON

Methods	Running Time
Manual approach	35 minutes
Uniform spatial sub-sampling	24 minutes
Vector quantization algorithm	19 minutes
Stratified sampling	11 minutes
Matsopoulos's method	4.5 minutes
The proposed method	< 1 minute

Laliberte proposed a retinal image registration and fusion method in [12]. 10 threshold parameters of which 7 are dependent on the image resolution and 3 left main free were reported. More threshold parameters, more human's interaction required when the parameters have to be adjusted, and hence less automation level the program is. In the new registration and fusion program, there are 9 adjustable threshold parameters. Among them, 5 are dependent on the image resolution/size and 4 are left main free.



(a) (b)



(c) (d)

Fig. 4: Fused image improvement during the iteration
(MPC (a) = 30732, (b) = 30888, (c) = 31134, (d) = 32277)

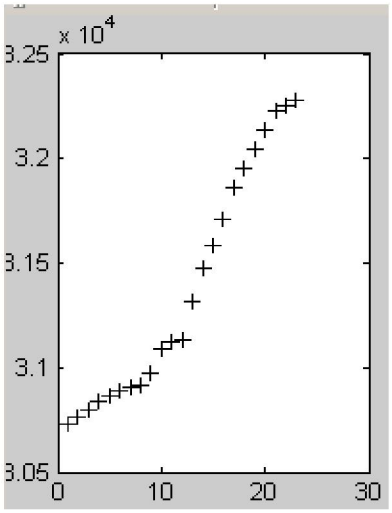


Fig. 5: MPC increasing during the iteration.
Y-axis is the MPC value; X-axis is the loop count.

V. CONCLUSIONS

An automatic approach for multi-modality retinal image registration using feature-based method has been developed. This approach is very efficient and robust to handle multi-sensor retinal image registration as long as the input image, compared with the reference image does not have large rotation or translation. The drawback, which common feature-based approaches have to deal with, is that if there is a huge rotation or translation of the input image, one has to implement area-based registration method to align the image beforehand. The feature-based multi-modality registration algorithm presented serves as a fundamental step for the hybrid area-based and feature-based systems. Thus the new approach is a promising step towards useful clinical tools for retinopathy diagnosis, which forms a good foundation for further development.

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