



Retinal image registration as a tool for supporting clinical applications

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ABSTRACT

Background and Objective: The study of small vessels allows for the analysis and diagnosis of diseases with strong vasculopathy. This type of vessels can be observed non-invasively in the retina via funduscopy. The analysis of these vessels can be facilitated by applications built upon Retinal Image Registration (RIR), such as mosaicing, Super Resolution (SR) or eye shape estimation. RIR is challenging due to possible changes in the retina across time, the utilization of diverse acquisition devices with varying properties, or the curved shape of the retina.

Methods: We employ the Retinal Image Registration through Eye Modelling and Pose Estimation (REMPE) framework, which simultaneously estimates the cameras' relative poses, as well as eye shape and orientation to develop RIR applications and to study their effectiveness.

Results: We assess quantitatively the suitability of the REMPE framework towards achieving SR and eye shape estimation. Additionally, we provide indicative results demonstrating qualitatively its usefulness in the context of longitudinal studies, mosaicing, and multiple image registration. Besides the improvement over registration accuracy, demonstrated via registration applications, the most important novelty presented in this work is the eye shape estimation and the generation of 3D point meshes. This has the potential for allowing clinicians to perform measurements on 3D representations of the eye, instead of doing so in 2D images that contain distortions induced because of the projection on the image space.

Conclusions: RIR is very effective in supporting applications such as SR, eye shape estimation, longitudinal studies, mosaicing and multiple image registration. Its improved registration accuracy compared to the state of the art translates directly in improved performance when supporting the aforementioned applications.

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1. Introduction

Diseases with strong vasculopathy, like hypertension [1] and diabetes [2] can be diagnosed and monitored through the analysis of small vessels. Such analyses can be performed in the retina, as it provides an easy and non-invasive way to assess the microvascular status via funduscopy [3]. Additionally, the diagnosis of illnesses that affect the eyesight, like glaucoma, age-related macular degeneration or macular edema [3] can be performed via the study of retinal structures. Images of the retina can typically be acquired utilizing fundus cameras, or Optical Coherence Tomography (OCT) [3] devices.

Depending on the task at hand, analysing retinal images can be eased by Retinal Image Registration (RIR) [4]. Image registration is

a technique in which, given a pair consisting of a test and a reference image, the test image is transformed so that its points are co-located with the corresponding points in the reference image. The images in the pair can differ with respect to their viewpoint, acquisition time and acquisition device.

RIR can be utilized as a stepping stone for developing several applications that aim to facilitate the analysis of the retina by clinicians. Such applications range from increasing the retinal area displayed by an image, to enhancing the quality of the picture, estimating geometrical characteristics and even tracking changes across time such as the thinning of blood vessels. Traditionally, RIR has been employed mostly to perform image mosaicing [5–7]. This practice consists of aligning retinal images from different parts of the retina to create a single representation corresponding to a wider field of view (FOV). Typically, mosaicing is performed with images with a small overlap that are acquired during the same examination session. Most of the old fundus cameras have a narrow

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FOV, therefore mosaicing is very important for studying properly the retina.

The main purpose of registering retinal images from different time periods is to perform longitudinal studies, allowing to monitor the evolution of retinopathy in the patient [8–10]. This can be used both to track the usefulness of a treatment (to be able to see if and how fast the patient recovers), as well as to follow the evolution of the sickness in untreated patients. Ways to do this would be to compare variations in vessel diameter at the same anatomical points, to observe the growth of cotton-wool spots or to analyse the increase of vessel tortuosity.

Multi-frame Super Resolution (SR) methods utilize multiple images of the same scene acquired from slightly different viewpoints to produce an image of higher resolution and definition [11–14]. In fundoscopy, imaging the retina from slightly different perspectives, even when attempting to image the same surface, is inherent due to saccadic motion. Image registration constitutes the basis of SR methods because it enables the utilization of pixel values from different images as additional samples at a certain location.

Registered retinal images can be used to perform 3D reconstructions of the retinal surface [15–18] and/or its vessel trees [19,20]. As with SR, these reconstructions and estimations can assist clinicians in the form of more precise measurements of diverse elements in the retina.

In this work, our goal is to show quantitatively the suitability of the Registration through Eye Modelling and Pose Estimation (REMPE) [21,22] framework when applied to SR and eye shape estimation. Additionally, we provide indicative results demonstrating that its utilization for longitudinal studies, mosaicing, and multiple image registration is also a possibility. An extensive evaluation of the accuracy and reliability of the registration framework is provided in [21,22].

2. Experimental setup

In the experiments carried out within this work, the REMPE [21,22] framework is utilized for performing RIR on retinal image pairs on a variety of datasets.

2.1. The REMPE framework

The REMPE framework [21,22], which is publicly available¹ is based on the simultaneous estimation of the relative 3D pose of the cameras that acquired the retinal images to be registered, as well as the shape and orientation of an ellipsoidal model of the eye. Fig. 1 shows the image acquisition and registration geometry in REMPE. An overview of the REMPE workflow is shown in Fig. 2.

To perform retinal image registration, we rely on Scale-Invariant Feature Transform (SIFT) and bifurcation matches, as combining these types of features provides increased accuracy [23]. Bifurcations provide keypoints located in the blood vessels of the retina, while SIFT allows to find and match keypoints in the optic disc, the fovea, in areas with other features, such as haemorrhages or cotton wool spots, as well as in the vessels themselves. Keypoints are projected onto a spherical eye model to perform an initial camera pose estimation using Random Sample Consensus (RANSAC) [24].

The ellipsoidal shape of the eye is represented as $\{\mathbf{A}, \mathbf{Q}\}$, with $\mathbf{x}^T \mathbf{Q}^T \mathbf{A} \mathbf{Q} \mathbf{x} = 1$, where $\mathbf{x}$ is a point on the eye model surface. Ellipsoid $\mathbf{A}$ is represented with 3 orthogonal semi-axes as

$$\mathbf{A} = \begin{bmatrix} a^{-2} & 0 & 0 \\ 0 & b^{-2} & 0 \\ 0 & 0 & c^{-2} \end{bmatrix}, \quad (1)$$

and rotations $\mathbf{Q} = \mathbf{R}_a(r_a) \cdot \mathbf{R}_b(r_b) \cdot \mathbf{R}_c(r_c)$ of said semi-axes.

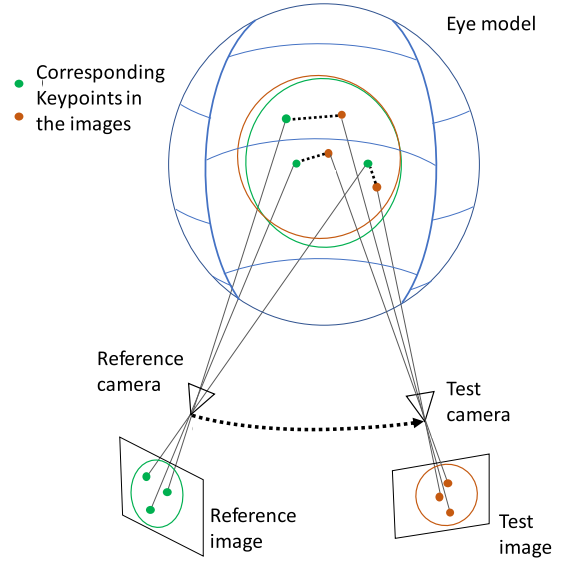


Fig. 1. The geometry of image acquisition and registration in REMPE.

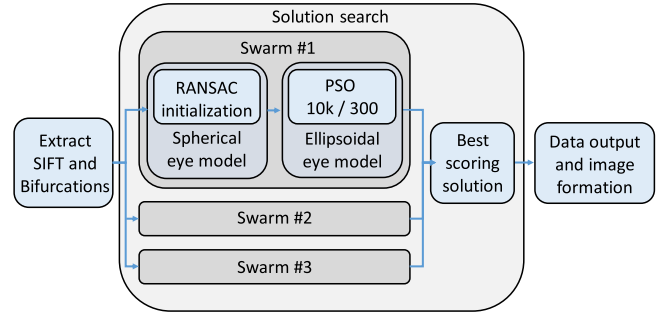


Fig. 2. Workflow of the REMPE framework.

The projection of the keypoints to the spherical model is achieved by considering the visual ray from eye center $\mathbf{c}$, through image keypoint $\mathbf{u}$. Let point $\mathbf{x}$ be the intersection of this ray with the image plane. The 3D coordinates of $\mathbf{x}$ are given by $\mathbf{x} = P^+ \mathbf{u} + \lambda \mathbf{c}$ by solving the ray's equation $P^+ = P^T (P P^T)^{-1}$ (see [25, p. 162]) for λ , where $\mathbf{c}$ is the camera center and P the projection matrix.

The pose is subsequently refined by utilizing Particle Swarm Optimization (PSO) with an ellipsoidal model of the eye for which the shape and orientation parameters are also estimated [26]. PSO is a method that utilizes a number of particles randomly distributed across the problem's search space, that evolve through iterations converging towards the location of the particle that provided the best solution up to the current generation. PSO is a stochastic derivative-free method that prevents discretization of the problem, thus allowing for more accurate solutions. Moreover, it requires the configuration of very few parameters and has been shown to perform remarkably well even in high-dimensional optimization spaces.

The time complexity of the algorithm that utilizes i swarms, p particles, g generations and k keypoints is $O(i \cdot p \cdot g \cdot k)$. This large computational complexity, caused mainly due to the utilization of PSO, is alleviated in practice due its high speed CUDA implementation.

2.2. Datasets

Six different datasets, each of them with diverse characteristics regarding image resolution, FOV and color modes (grayscale

¹ <https://projects.ics.forth.gr/cvrl/rempe/>

or color) have been utilized in the experiments presented in this work.

- The Fundus Image Registration (FIRE) [27] dataset²: Consists of a collection of 129 color retinal images forming 134 image pairs that have been classified into 3 categories depending on the session on which they were taken and the absence or presence of anatomical differences. Ground truth for registration is provided.
- The RODREP [28] dataset: Provides a large amount of images retrieved following a screening program in which for 140 eyes, 2 sets of 4 color pictures are acquired. In these sets of 4 images, there is very limited overlap, as the purpose is to generate image mosaics. There are no image pairs with anatomical differences and no ground truth is provided.
- The e-optha [29] dataset: Provides 144 color image pairs, both with large and small overlaps of the retina. Similarly to RODREP, there are no image pairs with anatomical differences and no ground truth is provided.
- The VARIA [30] dataset: Provides 154 grayscale image pairs. The FOV of the images is small, all image pairs have a large overlapping area of the retina, and no ground truth is provided. Thus, this dataset is quite limited for the purpose of retinal image registration.
- The *SR1* (Super Resolution dataset 1): Consists of a subset of 9 fundus images with large overlapping area extracted from the FIRE dataset.
- The *SR2* (Super Resolution dataset 2): Contains 9 grayscale images obtained with a Heidelberg Scanning Laser Ophthalmoscope (SLO). Images were provided by Dr. Maged Habib from the Sunderland Eye Infirmary, United Kingdom.

2.3. Experiments

The suitability of utilizing REMPE in five applications of RIR is explored. Experiments are divided into quantitative (for the cases of SR and eye shape estimation) and qualitative ones (for the cases of multiple image registration, longitudinal studies and mosaicing).

3. Quantitative experiments

3.1. Super resolution

In this work, while we do not focus on the suitability of multi-frame SR for obtaining images of higher resolution and definition, we demonstrate that the REMPE RIR framework leads to improved SR images when compared to using other, state-of-the-art RIR methods. We have comparatively evaluated REMPE with Generalized Dual Bootstrap-Iterative Closest Point (GDB-ICP) [31] and Partial Intensity Invariant Feature Descriptor (PIIFD) on Harris corners [6]. For SR, the MATLAB implementations³ for the methods presented in [32], [33] and [34] as well as interpolation of image points were utilized.

Multi-frame SR is quantitatively evaluated in relevant literature with a range of metrics. In [35] both Structural Similarity (SSIM) and Mean Square Error (MSE) are utilized. Peak Signal-to-Noise Ratio (PSNR) is used in [36]. Signal-to-Noise Ratio (SNR) is employed in [37]. As these methods require to compare with a reference image, the typical procedure is to reduce the size of the images to register, so that the resulting SR image is of equal size to the original reference image. In this case, the images were resized to one third of their original size and SR was performed with a scaling factor of 3.

Table 1

SNR for SR comparison in *SR1*. Bold shows the best score.

Method	[32]	[33]	[34]	Interpolation
REMPE	56.568	56.515	55.973	56.515
GDB-ICP [31]	55.420	55.257	54.507	55.256
Harris-PIIFD [6]	39.385	39.308	33.827	39.307

Table 2

PSNR for SR comparison in *SR1*. Bold shows the best score.

Method	[32]	[33]	[34]	Interpolation
REMPE	2.960	2.942	2.373	2.942
GDB-ICP [31]	2.526	2.454	1.792	2.453
Harris-PIIFD [6]	-4.862	-4.893	-7.003	-4.894

Table 3

SSIM for SR comparison in *SR1*. Bold shows the best score.

Method	[32]	[33]	[34]	Interpolation
REMPE	0.932	0.930	0.930	0.930
GDB-ICP [31]	0.930	0.929	0.929	0.929
Harris-PIIFD [6]	0.881	0.879	0.859	0.879

Table 4

MSE for SR comparison in *SR1*. Bold shows the best score.

Method	[32]	[33]	[34]	Interpolation
REMPE	189.658	190.009	201.124	190.004
GDB-ICP [31]	198.072	199.516	213.162	199.528
Harris-PIIFD [6]	414.664	415.958	513.653	415.985

Table 5

SNR for SR comparison in *SR2*. Bold shows the best score.

Method	[32]	[33]	[34]	Interpolation
REMPE	100.299	98.622	99.260	101.252
GDB-ICP [31]	83.167	84.056	78.988	84.892
Harris-PIIFD [6]	-8.240	-8.423	-8.261	-8.394

Table 6

PSNR for SR comparison in *SR2*. Bold shows the best score.

Method	[32]	[33]	[34]	Interpolation
REMPE	10.684	9.876	10.164	11.177
GDB-ICP [31]	2.247	2.710	0.122	3.120
Harris-PIIFD [6]	-28.285	-28.314	-28.307	-28.303

Table 7

SSIM for SR comparison in *SR2*. Bold shows the best score.

Method	[32]	[33]	[34]	Interpolation
REMPE	0.956	0.960	0.956	0.969
GDB-ICP [31]	0.795	0.817	0.784	0.816
Harris-PIIFD [6]	0.636	0.626	0.634	0.626

Results for dataset *SR1* are shown in Tables 1–4. Results for dataset *SR2* are shown in Tables 5–8. These tables show that for a given SR method, results are best when utilizing the REMPE RIR method. This stems from the fact that REMPE performs registration more accurately than the competing registration methods.

Fig. 3 shows the reference images, and Fig. 4 shows detail of the results for *SR1* and *SR2* utilizing the SR method from Irani and Peleg [32]. From left to right: reference image, REMPE, GDB-ICP [31] and Harris-PIIFD [6].

3.2. Eye shape estimation

These experiments were performed to validate the eye shape as this is estimated by the registration framework. Modalities such

² <https://projects.ics.forth.gr/cvrl/fire/>

³ <http://lcav.epfl.ch/software/superresolution>

Table 8
MSE for SR comparison in $SR2$. Bold shows the best score.

Method	[32]	[33]	[34]	Interpolation
REMPE	87.606	94.978	92.285	83.393
GDB-ICP [31]	203.691	194.471	251.922	186.658
Harris-PIIFD [6]	4314.5	4327.1	4324.2	4322.3

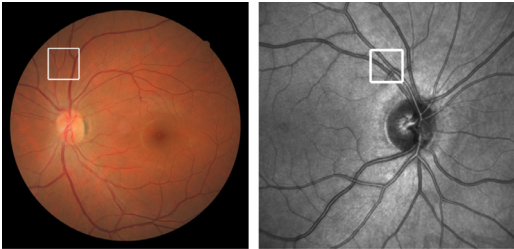


Fig. 3. Reference images for $SR1$ and $SR2$. White square indicates detail shown in Fig. 4.

Table 9
Error in the estimation of the lengths of eye axes in synthetic images. Error is indicated as the average of the percentage of the ground truth values.

	45°	100°
8 DoF search	0.25%	0.06%
9 DoF search	6.54%	0.52%

as OCT or Magnetic Resonance could provide ground truth for the actual shape of a given eye. However, such data is unavailable to us. Instead, synthetic images with known ground truth were generated.

Two sets of synthetic images were generated utilizing an ellipsoidal eye model. The images were generated utilizing the same ground truth but with different virtual cameras, with FOV of 45° and 100°, respectively. REMPE is utilized to estimate the relative pose of the cameras, as well as the lengths of the axes of the ellipsoidal eye model, but not the orientation of the ellipsoidal eye model, which is provided to the framework. For both datasets, the framework is run twice. In one run, all 9 parameters are estimated. In the other, one of the axes of the eye model is fixed to the ground truth, so that only 8 parameters are estimated. Results are shown in Table 9. When one of the axes of the eye model is

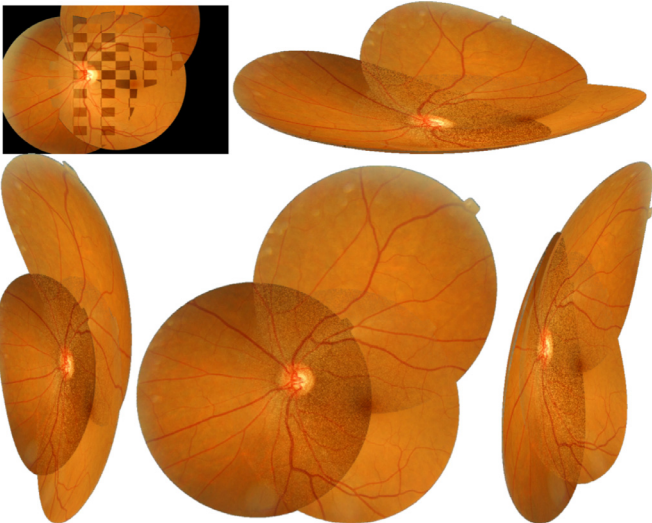


Fig. 5. 2D and 3D results of simultaneous registration of multiple images. 3D results display a color pointcloud.

known, the framework is able to correctly estimate the parameters with high accuracy for both FOVs. However, when the three axes from the eye model are unknown, the framework is not able to estimate the axes of the ellipsoidal eye model for a FOV of 45°. These results prove that with a wide field of view, the framework is able to perform 3D registration with an accurate estimation of the eye model. If the Navarro eye model [38] is utilized, where the eye axes measure 24 mm diametrically, that means an average error of 0.06 mm per axis. However, for 45°, which is the FOV of interest in this work, the error grows to 0.78 mm per axis.

This eye shape estimation error is seen in synthetic images that were generated using an eye model with a smooth surface. In real images, the retinal surface is irregular. The impact of this surface irregularity in the 3D keypoint localization and shape estimation leads us to believe that the error in the shape estimation will be larger in real images than in synthetic ones. Given the need of clinicians for accurate measurements, we believe that at this stage of the research the performance of measurements using real distances (i.e. mm) in the 3D estimated models is not yet accurate enough, but they show great potential.

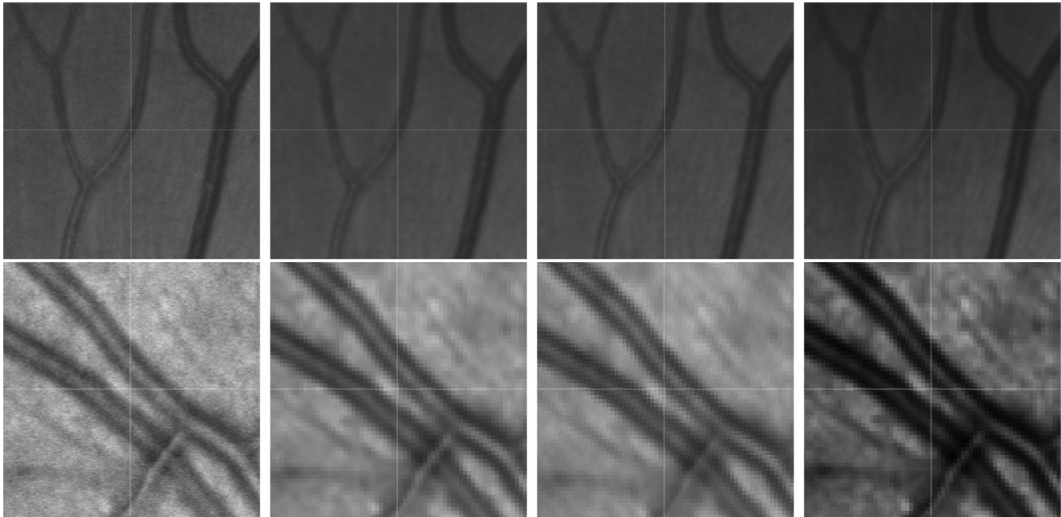


Fig. 4. Detail of SR results for $SR1$ (top) and $SR2$ (bottom). From left to right: reference image, REMPE, GDB-ICP [31] and Harris-PIIFD [6].

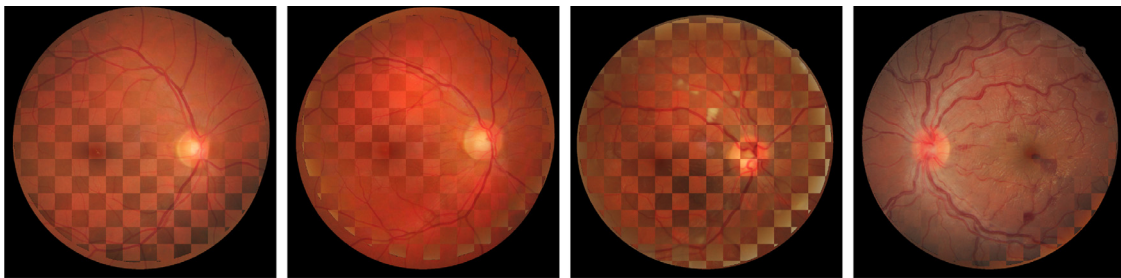


Fig. 6. Longitudinal registration results for the FIRE dataset. The 2 images on the left show registration results for image pairs with no anatomical differences, while the 2 images on the right show registration results for image pairs with anatomical differences. Results displayed in a checkerboard mosaic, alternating patches from both images, with the intent to show registration accuracy, not for analyzing anatomical differences in the registered images.

Table 10

Average registration time per image, in seconds [21].

Method	REMPE	GDB-ICP [31]	Harris-PIIFD [6]
Time (s)	198	73	11

A qualitative result of eye shape estimation performed on a set of 3 real images is shown in Fig. 5 and in video forms both in the supplementary material and in YouTube.⁴

3.3. Execution time

This experiment compares the execution times of the REMPE method, with GDB-ICP [31] and Harris-PIIFD [6], which are the competing methods utilized in Section 3.1. Experiments were run in an Intel Core i7-4770 CPU @ 3.40 GHz with 16 GB of RAM memory and a NVIDIA GeForce GT 730. Results are presented in Table 10 [21]. While REMPE is the slowest method, analysis from Section 3.1 shows that it provides more accurate registration than the alternatives. Additionally, it is not prohibitively large to be used in examination sessions. Moreover, as seen in Section 3.2, REMPE

estimates the eye shape and generates a colored 3D point mesh, while competing methods merely perform 2D-2D registration.

4. Qualitative experiments

4.1. Multiple image registration

This experiment aims to demonstrate qualitatively that the REMPE RIR framework allows for the simultaneous registration of multiple test images to a single reference image. While this can be performed in 2D with multiple pairwise registrations of test images to the reference image, this task is not trivial for the case in which eye shape estimation is also performed, as this requires a simultaneous 3D registration. The simultaneous registration presented here demonstrates that REMPE allows for the combination of information from multiple images to perform a single registration and eye shape estimation. Thus, it allows to estimate a single retinal surface and to register all images to it in 3D.

Experiments have been performed utilizing images from the RODREP [28] dataset, which has been compiled with the purpose of performing registration of multiple images from the same eye for creating mosaics and, therefore, is the most suitable dataset for this purpose. Fig. 5 and the previous experiment's video⁴ show qualitative results for this type of multiple registration.

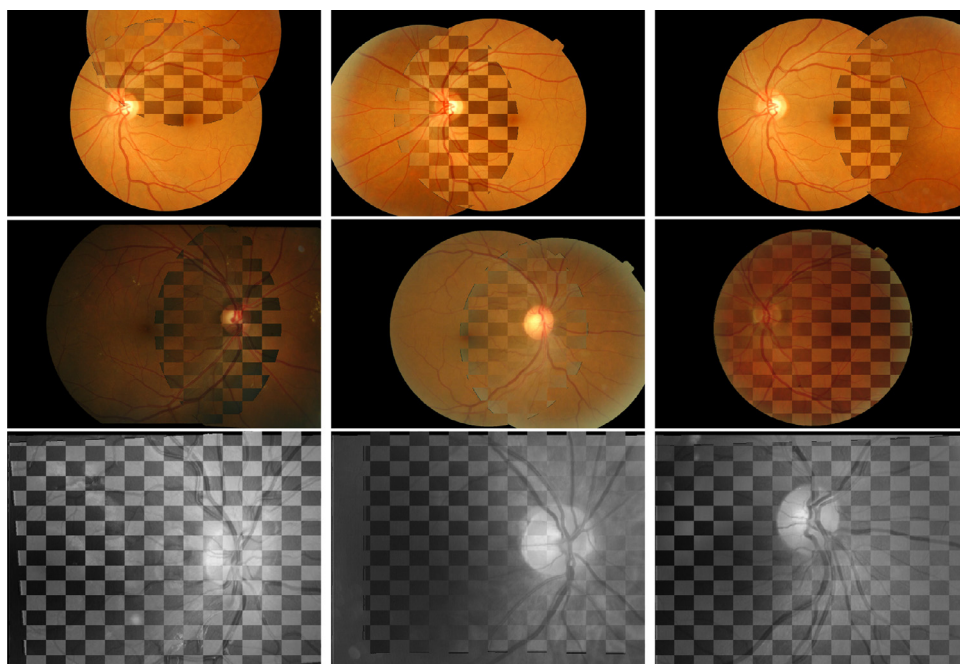


Fig. 7. Mosaic registration results for the RODREP (top), e-optha (middle) and VARIA (bottom) datasets. Figure interpretation in Fig. 6.

4.2. Longitudinal studies

These experiments evaluate the applicability of REMPE for supporting longitudinal studies. Fig. 6 shows registration results for 4 image pairs of the FIRE [27] dataset. The 2 images pairs on the left contain no anatomical differences, while in the 2 image pairs on the right there exist anatomical differences within each image pair.

These results show that REMPE performs accurate registration for image pairs in which there may exist anatomical differences. This is an important tool for clinicians, as it may facilitate visual analysis of image pairs to detect retinal changes such as early arteriolo-sclerosis, which is important for early diagnosis of hypertension.

4.3. Mosaicing

These experiments show mosaicing results using REMPE for 9 image pairs from 3 of the employed datasets. Fig. 7 displays results for 3 image pairs from each of the RODREP [28], e-optha [29] and VARIA [30] datasets.

These results show that the REMPE framework performs accurate registration for image pairs with a wide range of characteristics. Image pairs may present varying degrees of overlap, FOV, resolution and they may even be monochromatic. Mosaicing is an important tool for clinicians, so providing accurate mosaics is of utmost importance for a RIR framework.

5. Conclusion

Applications with clinical purposes such as SR, eye shape estimation, longitudinal studies, mosaicing and multiple image registration can be built on top of techniques that achieve retinal image registration. The higher the accuracy of the registration, the better the end results for these applications.

In this work, we demonstrated the suitability and the effectiveness of REMPE [21,22] for such applications. REMPE is quantitatively shown to outperform state-of-the-art methods when utilized to register images to be used with multi-frame SR methods. A study on eye shape estimation was also presented. We believe this has the potential to improve the measurements in which clinicians base their diagnoses, opening the possibility to perform measurements on 3D representations of the eye, instead of doing so in 2D images that contain distortions induced because of the projection on the image space.

Additionally, its application for multi image registration, longitudinal studies and mosaicing is indicated. Results in 2D and 3D for simultaneous registration of a triple of retinal images is shown. For longitudinal studies, qualitative results are shown both for image pairs with and without anatomic differences. For mosaicing, qualitative results are shown for REMPE when registering images across different publicly available datasets.

Experiments have been performed over 6 different datasets, showing the flexibility of the REMPE framework to accomplish accurate RIR on images with very diverse characteristics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at [10.1016/j.cmpb.2020.105900](https://doi.org/10.1016/j.cmpb.2020.105900).

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