A multiscale elastic registration scheme for retinal angiograms

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Received 15 February 2002; accepted 30 March 2004
Available online 17 June 2004

Abstract

The present paper describes a new and efficient method for registration of retinal angiogram. The presence of noise, the variations in the background, and the temporal variation of fluorescence level poses serious problems in obtaining a robust registration of the retinal image. Here, a multiscale registration scheme is proposed which comprises of three steps. The first step of this work proposes an edge preserving smoothing of the vascular tree. This morphological filtering approach is based on opening and closing with a linear rotating structuring element. For complete preservation of the linear shape of the vascular structures, a morphological reconstruction by dilation of the opened image and a reconstruction by erosion of the closed image are applied. It is proposed to compute the registration transform between two successive original frames, from their morphological gradient. Then, the second step consists in computing the morphological gradient of the two filtered images and radiometrically correcting these gradient images. To take into account the intensity variations, our model incorporates two constant multiplicative and additive factors (based on contrast and brightness) estimated employing a simple analysis of the local histograms (based on a sliding window). In the third step, the proposed method computes the registering transform through a coarse-to-fine (or multiscale) hierarchical approach. After computing the dominant registering transform (which implies the translation) between two successive frames, an elastic transform (also called local affine transform) is carried out to achieve a residual correction. The proposed method is tested by experimental studies, performed on macular fluorescein and Indo cyanine green angiographies. It has been sufficiently demonstrated that our proposed registering method
is robust, accurate and fully automated, and it is not based on the extraction of the features or landmarks.

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Keywords: Image registration; Optical flow; Mathematical morphology; Multiresolution; Retinal angiography

1. Introduction

The availability of a method for automatic registration of retinal angiogram will be of major assistance for clinical persons, both as diagnostic tools as well as screening help. This paper describes a method for automatic registration of the fluorescein and Indo Cyanine Green (ICG) angiograms.

1.1. Retinal angiogram images

1.1.1. Ocular fundus angiography

Fluorescein and ICG angiograms are both useful in the diagnosis and treatment approaches of many retinal diseases like age related macular degeneration (ARMD) and diabetic retinopathy (DR). Retinal angiography (up to 36 frames) [1] is usually divided into three phases, early, mid, and late. A reference fundus photograph (Fig. 1), red free frame, is taken without dye, using a green filter. The early phase of the dye circulation of the angiogram can be broken down into distinct circulation phases that are useful for interpreting the results:

- **Arterial phase.** The retinal arteries are typically filled 1 or 2 s after the choroidal flush.
- **Arteriovenous phase.** Complete filling of the retinal capillary bed follows the arterial phase and the retinal veins begin to exhibit laminar flow.
- **Venous phase.** Complete filling of the large retinal veins occurs over a period of next 10 s. With the occurrence of the maximum vessel fluorescence within 30–35 s after the injection.

![Fig. 1. Fluorescein angiographic successive images of ocular fundus taken by conventional angiography. (A) Original image before injection. (B) Original image in the arterial phase.](image-url)
• **Late phase**, also known as the recirculation phase, takes place about 2–4 min after the injection. The veins and the arteries remain at approximately equal brightness. The intensity of the fluorescence diminishes slowly. It should be noted that the late phase or the elimination phase demonstrates the gradual elimination of dye from the retinal and the choroidal vasculature. Late staining of the optic disc is a normal finding in this phase. Any other areas of late hyperfluorescence suggest the presence of an abnormality. The interpretation of these abnormalities relies on the identification of areas that exhibit hypofluorescence or hyperfluorescence. These are descriptive terms that refer to the exact time for specific, relative brightness of fluorescence in comparison with a normal study.

### 1.1.2. Image quality

The temporal registration is necessary to detect and quantify the macular degeneration. The vessels are the only significant visible structures [1] in all the images used in our angiographic registration. However, there are many difficulties, e.g., non-uniform background of the image, the eye movements, various kinds of noises, and the presence of blood vessels—some of which, due to local intensity variations, may appear to have non-connected endings.

In the majority of the previously published works on automatic registration of the retinal images [2–9], it was assumed that the extractions of the features or the landmarks are previously known.

Since angiographic data may vary considerably in intensity (e.g., the blood vessels are dark before injection and in the early angiographic phase, but bright in the late angiographic phase) intensity based registration algorithms are unsuitable. We have explored the edge-based registration algorithms, and have demonstrated the acquisition of successful images of angiographic data, following image pre-processing with smoothing, and edge detection using morphological tools.

### 1.2. Morphological filtering

The filtering step will allow a more robust registration of the images. Image enhancement through noise reduction (also called image cleaning) is a fundamental problem in image processing. The first stage attempts to obtain edge-preserving filtering of the vascular structure, to permit angiographic registration. Here, it is assumed that the vessels have an elongated shape with an almost uniform orientation but a variable diameter in spatio–temporal image.

#### 1.2.1. Morphological filtering

Morphological filters are the most well-known non-linear filters for image enhancement [5,8–11]. Morphological filtering of an image involves transforming the image into another image using a structuring element that determines which are the geometrical features to be preserved in the filtered image [5,9–14].

The action of a morphological filter depends on its structuring element. Using appropriate combinations of the structuring elements and the morphological operation, spatial features in an image can be extracted, suppressed or preserved.
The choice of the structuring element, to be used in the morphological tools, is crucial because it determines both the extent and the “type” of smoothing that take place. Morphological openings and closings are useful for the smoothing of the grey-scale images [5,9–13,15–17]. However, their usage for the reduction of the noise in an image is limited by their tendency to remove important, thin features from an image along with the noise. These drawbacks can be overcome by using linear structuring elements, and by opening (or closing) the image in several separate directions and taking the superior (or the inferior).

Several filters have also been developed that selectively enhance those vessels which use their tubular shape. These methods are user-dependent, and cannot overcome the problems associated with the overlapping of the vessels with one another and with other anatomical structures. Once this directional filtering is successfully carried out, some works [9,11,13,17] proposed filtering using morphological reconstruction. With this directional smoothing, noise is eliminated, while the edges of the vessels are kept intact.

1.2.2. Multiscale morphological filtering

The main problem of using morphological filters is the selection of an appropriate structuring element. The shape of the structuring element plays a crucial role in extracting features or objects of given shape from the image. However, for an extraction of the features or the objects, based on shape as well as size, a second attribute must be incorporated for the structuring element, which is its scale [10,12]. A large structuring element will remove some perceptually sensitive details, while a small structuring element cannot efficiently simplify large image components. A morphological operation with a scalable structuring element can extract features based on shape and size simultaneously. Also features of identical shape but of different size are treated separately. The multiscale morphological enhancement utilizes a group of structuring elements.

Sternberg [18] introduced the idea for reduction of image noise through an iterative application of the openings and the closings employing successively larger structuring elements in each iteration. This technique, called an “alternating sequential filter” by Serra [19], is efficient for recovering some approximation of a structure that is nearly invisible in dense, high amplitude noise.

Another important concept in mathematical morphology is that of multiscale filtering. Chen and Yan [20] used a variable size structuring element to perform various morphological operations.

Song and Delp [21] have defined a technique which they called the “generalized morphological filter.” It takes linear combinations of the results of the openings and the closings with multiple structuring elements. This filter works well in presence of dense noise but there is a trade-off between the noise smoothing and the detail preservation.

The multiscale representation can be obtained by applying a series of smoothing filters, of increasing size, to an image. Multiscale smoothing, using morphological openings or closings, has been suggested for applications such as shape-size distributions, pyramidal image representations, and edge enhancement [14,22–24].
Floreby et al. [25] have developed a noise removal technique using morphological pyramid decomposition. A modified reconstruction multiscale morphologic edge detector was suggested by Chanda et al. [26].

There are other tools which have been proposed for morphological image cleaning (MIC) [10]. The main difference of the MIC with the previous morphological noise filters is that it manipulates residual images—the differences between the original image and morphologically smoothed versions. It calculates the residuals on a number of different scales, utilizing morphological size distribution [5].

A hierarchical image fusion scheme has been proposed by Matsopoulos et al. [27] that integrates features extracted from morphological pyramids of the multimodal images.

1.3. Image registration

During any angiographic sequence, there is inevitably eye movement and it is essential to make a correction prior to the application of the quantitative analysis. Automated registration of the retinal images will enable accurate comparisons between the images and will provide the ability to automate the calculation of the changes for both the lesions and the normal anatomic structures.

Most common search strategies have been used in motion analysis and image registration problems [7,12,15,16,28–30]. One common approach in most of these strategies is the application of a multiresolution method [29,30] based on optical flow, where the search is performed at increasingly higher resolutions. An important area of use of medical image registration is for retinal images [2]. To perform the reliable registration of the retinal images, features extraction is generally employed [2]. However, our registration method need not utilise features extraction.

Independent of the chosen technique, the estimation of the motion between two images [4,28–30] are most frequently based on the underlying assumption that the difference between the images are due to the motion only. This hypothesis ignores other possible causes for the difference between the images, such as variations in the ambient illumination, which is well-known for retinal angiographic images.

1.3.1. Optical flow technique

The two main definitions of motion estimation [16,28,31,32] are:

- The 2-D motion field, or “projected motion,” is the (perspective or orthographic) projection of the motion in real world scenario on the 2-D image plane.
- The optical flow is the field in image plane that is associated with the spatio–temporal variations of intensity pattern.

Several optical flow techniques have been proposed for motion analysis [16,28,30–32] including instances of differential methods, region-based matching, energy-based and phase-based techniques in [31].

There are four main groups of algorithms for estimation of 2-D motion:

- gradient-based motion estimation (including pel-recursive and Bayesian-based techniques),
- block-based motion estimation (including the phase correlation method),
• model-based or parameter-based motion estimation,
• frequency-domain motion estimation.

The classical optical flow approach generates motion fields between successive images. Using filtered and gradient images, this method will be particularly robust in terms of changes in intensity and noise between images. The method was successfully applied to temporal retinal image pairs.

Frequently, the estimation of motion between two consecutive images is based on the underlying assumption that the difference between the images is due to motion only. This hypothesis ignores other possible causes of the difference, such as variations of the illumination.

Some methods of motion analysis [4,5,10,28–30,33] have been demonstrated to be robust in presence of time-varying illumination.

1.3.2. Gradient-based motion estimation

In this technique, the optical flow can be estimated from the values of the intensity gradient of the spatio–temporal image, by using the appropriate spatio–temporal global smoothness constraint or more advanced local smoothness constraints [30].

Multigrid extensions for large velocities are:
• the multiresolution analysis,
• low-pass Gaussian pyramids,
• band-pass Laplacian of Gaussian,
• wavelet pyramids,
• the coarse-to-fine and the fine-to-coarse strategy.

Coarse-to-fine (or multiscale) hierarchical approach has been employed by many researchers [30,32]. It has been shown that hierarchical estimation techniques can often achieve efficient and robust performance. These methods can provide an accurate estimation.

Conventional gradient methods (optical flow), for estimation of registration, assume conservation of intensity between frames. This assumption is often violated in retinal images because a gradient method (optical flow) is widely used in registration estimation [4,32,34]. The method assumes that the image intensity is kept along with the motion. This assumption produces constraints for the local transformation.

2. Methods

The difficulties associated with the angiographic registrations are the non-uniform background of the background, various kinds of noises, the intensity variations of the blood vessels during the retinal angiographic sequence, and finally the eye movements.

Since the images are very noisy and the vessels are extremely narrow, we have developed a registration algorithm, which does not require to extract complete or non-complete vessel trees or to detect landmarks.

The strategy of the presented method is to filter images before registration, to compute their morphological gradient, and then to radiometrically register the gradient images and finally to compute the registering transform of these images.
Therefore, we have employed noise removal through morphological operators, and computed the morphological gradient, to calculate the multiscale registration transform, rather than from original images.

Multiresolution approaches provide a natural hierarchy of the data, allowing the coding to be performed at different spatio–temporal or quality resolutions. This is the concept associated with scalability. Several types of multiresolution decompositions have been studied in the past, most of them being the linear ones. This is the case for the pyramidal decompositions like the Laplacian and Gaussian pyramids, and wavelets.

2.1. Morphological filtering

Morphological operators are particularly interesting for several tasks like filtering [12,13,16], segmentation [8,9], and feature extraction. Grey-scale mathematical morphology methods are used to process fundus image, to enhance blood vessels and to filter out noise [9,13]. The vessels can be modelled as dark or bright tubes of varying diameters.

We did not apply these multiscale morphological operators (more complex like the classical methods) although they are successful. Needing only the gradient images for the registration, the classical morphological filters (open and close) with a linear rotating structuring element have been sufficient to filter out noise in angiographic images.

To enhance the results obtained during filtering, we have used the morphological reconstruction by erosion and by dilation [9,17].

These retinal angiogram images are characterized by poor local contrast. Fig. 1 shows an example of two successive images, which were taken from fluorescein angiography. Since the images are very noisy, a registration step requires a filtering stage of the retinal vascular tree.

In this study, a morphological filtering has been implemented, using a linear rotating structuring element [9,11,13,17], to filter the vascular network. A series of morphological openings/closings with different directions are performed to remove the noise from the frames.

The classical morphological filters: opening \((\gamma_B)\) and respectively closing \((\phi_B)\) with a structuring element \(B\) annihilate image features of which support (i.e., the area in the image) does not recover the structuring element. That is, they eliminate small features and thin features. On the other hand, these operations preserve features that can contain the structuring element.

A first kind of approach to vessel enhancement is based on the multiple rotation-invariant or linear morphological operators of proper sizes and orientations, which are applied to the image to remove background and noise. An advantage of such operators is their high selectivity to grey-level patterns, similar to the structuring element(s) adopted; a disadvantage is a remarkably high demand for computation.

It has been straightforward to show from the geometrical interpretation that the opening and the closing with a linear structuring element \(B\) of length \(p\) preserve those objects for which the width is larger than \(p\) in the direction of \(B\). In particular, very thin objects parallel to the direction of \(B\) are preserved.
To reduce the noise while preserving the linear features, the differential image is further filtered by employing a multidirectional morphological filter:

\[ I_o = \bigvee_{i=1}^{n} \gamma_{B_i}[I], \]

\[ I_c = \bigwedge_{i=1}^{n} \phi_{B_i}[I], \]

where \( \vee \) denotes pointwise maximum, \( \wedge \) pointwise minimum, \( \gamma \) and \( \phi \) denote morphological opening and closing respectively, with the linear structuring elements \( B_{i=1:n} \) according to \( n \) directions. \( I_o \) is the supremum and \( I_c \) is the infimum of these directional openings.

Thin bright (or dark) objects, locally parallel to one of the structuring elements are preserved. Results are shown in Fig. 2.

2.1.1. Morphological reconstruction

To completely preserve the linear shape of the vascular structures [9,11,17], we apply a morphological reconstruction (Fig. 3) by dilation (3) of the opened image and a reconstruction by erosion (4) of the closed image:

\[ g_{T}^{\text{Rec}}(I_o) = \bigvee_{n \geq 1} \delta_{I}^{(n)}(I_o), \]

\[ g_{T}^{\text{Rec}}(I_c) = \bigwedge_{n \geq 1} \varepsilon_{I}^{(n)}(I_c). \]
2.1.2. Morphological gradient

Since angiographic images contain non-uniform background, there are intensity variations of blood vessels during the retinal angiographic sequence, and finally we experience the variations in the intensity of the background. Thus, the morphological gradient (Figs. 4A and B) of two filtered images are computed and these two gradient images (Fig. 4C) are added to obtain one gradient image by angiographic image.

The morphological gradient $g$ of an image $I$ is defined as the difference between the dilated and the eroded image

$$g(I) = \delta(I) - \psi(I).$$  \hfill (5)

This ‘thick’ gradient can be decomposed into two ‘half’ gradients: an ‘inner’ gradient

$$g_-(I) = I - \psi(I),$$  \hfill (6)

adhering to the inside of the objects, i.e., the bright side of the edge; and an outer gradient

$$g_+(I) = \delta(I) - I.$$  \hfill (7)

2.1.3. Radiometric correction

Various phenomenological extensions to the brightness constancy constraint have been proposed to make it less restrictive. Negahdaripour and Yu [35] have proposed a generalized brightness change model for optical flow in which the additive and the multiplicative terms are spatially varying.
Recently, many methods have been proposed to cope with the problem of the variations in brightness [4,36,37]. Hampson and Pesquet [4] introduced an additional coefficient in their pel-recursive motion estimator to estimate both the motion and the illumination variation fields. Nomura [36] and Zhang and Blum [30] had successfully applied these two constraints in detecting the image motion fields under non-uniform or non-stationary illumination variations. Haussecker and Fleet [37] proposed some physical models of brightness variation, including the brightness variations caused by diffusion, moving illumination envelope or changed surface orientation, etc., for optical flow computation.

To improve registering estimation (Fig. 4D), we incorporate an explicit change of the local contrast and brightness into our model. Specifically, we propose to modify the global luminance of a gradient image compared to the other gradient image, like in [35]. Variation of intensity is typically a significant source of error in the estimation of differential motion. The addition of the contrast and brightness terms allows us to accurately register images in presence of the local intensity variations.

2.2. Multiscale image registration

The registering transform between successive image pairs is computed between gradient filtered images, rather than between original frames.

2.2.1. Optical flow technique

The optical flow field is estimated from the spatio–temporal variations in the intensity of the image. Several research efforts have proposed algorithms that compute optical flow from the spatial and the temporal derivatives of the image intensity.

The assumption of intensity conservation is only approximately true in practice. For example, the constant-intensity model developed with the help of a motion constraint equation is under-constrained and at the same time is often violated due to the factors such as noise, non-opaque surface reflections, occlusions or spatio–temporally varying illumination.

2.2.2. Coarse-to-fine estimation by least squares

In this paper, we present an approach to combine optical flow estimation methods with a degree-based registration approach.

First, a multiscale decomposition is applied to the source images to obtain two sets of gaussian pyramids. It is now well-known that the use of the multi-resolution schemes considerably improves the estimation of motion analysis using differential methods, i.e., using spatio–temporal gradients of intensity. This issue has been mainly studied and validated in dense optical flow field estimation [16,28,29].

Accurate estimations can be recovered even with large displacements or with an irregular distribution of the intensity gradient in the image. More recently, some authors [16,29,30] proposed a multi-resolution “least mean squares” technique for estimation of motion parameters.

A different approach for handling the non-constant intensity in the direction of motion is explicit modelling of the illumination [34]. This approach is promising,
although it requires complex minimization since, in addition to the motion field, also variations in illumination field must be estimated.

2.2.3. The translational motion model

A two-parameter translational motion model is first used for the object:

\[ p(x, y, t) = a, \quad q(x, y, t) = d, \]

where \( (p(x, y, t), q(x, y, t)) \) is the displacement induced on pixel \((x, y)\) by the motion of the object between frames \(t\) and \(t + 1\).

Assuming that the image intensity is invariant, \( I(x + p, y + q, t + 1) \) is equal to \( I(x, y, t) \). By using the Taylor series expansion, the following equation is obtained:

\[ p I_x + q I_y + I_t = 0, \tag{10} \]

where \(I_x, I_y, I_t\) are the partial derivatives of the intensity \(I(x, y, t)\) with respect to \(x, y, t\).

We look for a motion \((p, q)\) which minimizes the error function at frame \(t\):

\[ \text{Err}(p, q) = \sum_{(x,y) \in M} (p I_x + q I_y + I_t)^2, \tag{11} \]

where \(M\) is the object mask. Taking derivatives of \(\text{Err}(p, q)\) with respect to the parameters of translational motion and setting these derivatives to zero yield two linear equations in the two unknowns, \(m = (a, d)^T\), as follows:

\[ \begin{pmatrix} \sum I_x^2 & \sum I_x I_y \\ \sum I_x I_y & \sum I_y^2 \end{pmatrix} \begin{pmatrix} a \\ d \end{pmatrix} = -\begin{pmatrix} \sum I_x I_t \\ \sum I_y I_t \end{pmatrix}. \tag{12} \]

Let the \(2 \times 2\) matrix be \(A_t\) and the right-hand side column vector be \(b_t\). Then, this equation can be written as \(A_t m_t = b_t\). The translational motion vector \(m_t\) can be obtained as

\[ m_t = A_t^{-1} b_t = [m_t^x, m_t^y]^T. \tag{13} \]

We solve this system of equations by taking into account the whole image. The field of displacement is thus uniform.

2.2.4. The affine motion model

We use the six-parameter affine motion model for the object motion estimation:

\[ p(x, y, t) = a + bx + cy, \tag{14} \]

\[ q(x, y, t) = d + ex + fy, \tag{15} \]

where \( (p(x, y, t), q(x, y, t)) \) is the displacement induced on pixel \((x, y)\) by the motion of an object between frames \(t\) and \(t + 1\). The assumption of invariance of intensity for \(I(x, y, t)\) and \(I(x + p, y + q, t + 1)\) still holds valid.

Taking derivatives of Eq. 11 with respect to the parameters of the affine motion model of Eqs. 14 and 15 and setting them to zero yields six linear equations with six unknowns, \(m = (a, b, c, d, e, f)^T\), as follows:
Let the $6 \times 6$ matrix be $A$ and the right-hand side column vector be $B$. Then Eq. 13 can be written as

$$Am = -B. \quad (17)$$

We solve this system of equations by taking into account a region of interest (ROI).

### 2.2.5. The intensity variation model

The changes in the illumination have been modelled by constant multiplicative factor $v_1$ and additive factor $v_2$, i.e., $v_1I(x + p, y + q, t + 1) + v_2 = I(x, y, t)$. They have been automatically estimated by simple analysis of the local histograms of sliding window. Given an $N$ by $N$ image, let us consider a local histogram over an $M$ by $M$ sliding window. $v_1$ and $v_2$ are computed from histogram of two sliding windows at $t$ and $t + 1$ times to account for the multiplicative and additive deviations.

### 2.3. Algorithm

The proposed algorithm can be summarized in three steps:

- morphological filtering of the vascular network,
- morphological gradient computing, and
- coarse-to-fine estimation.

#### 2.3.1. Morphological filtering

This filtering scheme (Fig. 5) is computed by the supremum of the openings and the infemum of the closings using linear rotating structuring element. Finally, we computed the reconstruction by dilation of the opened image and by erosion of the closed image. This morphological filtering by reconstruction preserves the vascular structures completely.

#### 2.3.2. Morphological gradient

The morphological gradients of the reconstructed opened image and the reconstructed closed image are computed, and the sum of these gradient images is computed. Finally, we register radiometrically the gradient image 2 at register (Fig. 6).

#### 2.3.3. Coarse-to-fine estimation

Once the filtering of the two successive frames, and the computing of their morphological gradients are carried out, then the registering transform can be computed
(Fig. 7). To increase the robustness of the geometric registration, this motion transform has been computed in two steps: first the dominant motion (global translation), and then the residual motion (elastic).

The registration scheme of the retinal angiographic sequence begins with the first two successive frames. The scheme is repeated successively until the latest image. For each image pair, the registering transform is applied to the image at register.

After several iterative refinement steps of the optical flow estimation, using this decomposition level (more and more lower resolution), the process continues until the finest decomposition level is reached, and the final and the most accurate matching parameters are obtained.

The iterative refinement approach is used to obtain a more accurate global translation and elastic transformation within a given scale (level) and a more accurate global
Fig. 6. Morphological gradient scheme.

Fig. 7. Coarse-to-fine estimation.
translation and elastic transformation by successively moving to finer scales. The images are represented in multiple resolutions by constructing a Gaussian pyramid.

The assumption about the constancy of the intensity is usually approximately satisfied, but it is particularly violated when the illumination of the scene changes.

Similar transform estimations have been used with success for the registration of motion analysis. There are two benefits while using such an approach. The first is that a small number of parameters (six, in case of elastic flow) are enough to completely describe the flow vector at any point in the region of validity, which can be large, and that those flow vectors constitute a very good approximation of the real optical flow, as was shown by the studies mentioned above. The second interest is the low computation cost.

Starting at the lowest resolution level:
• transform parameters are estimated by solving the set of linear equations to minimize $\text{Err}(p, q)$, according to the appropriate motion model.
• the two images are registered by warping according to the computed motion parameters (steps 1 and 2) and are iterated at each resolution level for further refinement.
• the motion parameters are interpolated to the next resolution level, and are refined by using the higher resolution images.

First, the dominant 2-D global translation in the image pair is computed by applying a translation computation technique. Second, computation of a higher order parametric elastic motion is applied to improve the registering estimation.

3. Results and discussion

Choroidal neovascularization (CNV) associated with age-related macular degeneration leads to irreparable damage in the structure and the functioning of the retinal tissue. The patients suffering from exudative ARMD symptoms are sometimes examined with a scanning laser ophthalmoscope (SLO). The fluorescein angiography (FA) reveals place and time-dependent extent of the subretinal leakage and fluid, whereas, the ICG angiography may visualize the shape of the neovascular membrane. All angiographic images presented in this paper were digitized from the video signal output at a resolution of $1024 \times 1024$ pixels and with a quantization of 8 bits per pixel.

Our results demonstrate that our pre-processing with morphological filtering by reconstruction, morphological gradient, and radiometric registration allows a spatial registration of photographic and angiographic data, when the grey levels of the vessel may vary from black to white.

For our application, a morphological filtering of the vascular network has been computed with linear structuring element of size $3 \times 9$ pixels according to 16 directions.

Morphological reconstruction, by dilation of the opened image and by erosion of the closed image, has been computed. Finally, a morphological gradient by erosion with a hexagonal structuring element of size one has been chosen.

This hierarchical approach is a technique, which can often achieve efficient and robust performance for image registration. In coarse-to-fine estimation, our
decomposition is limited to five levels, so that the coarsest image level uses \( 64 \times 64 \) images for the \( 1024 \times 1024 \) source images we consider. Figs. 8–11 illustrate our registration results. First, a registration by the global translation model is applied and then the residual image transform is computed by an elastic model.

A number of popular measures: the sum of squared intensity differences (SSD), the sum of absolute intensity differences, cross-correlation, entropy of the difference image, ... These metrics are easy to compute and often affords simple minimization techniques. Many computer vision algorithms employ the sum of pixel-wise squared differences between the pair of images as a statistical measure of similarity. To evaluate the accuracy of our registration method, the sum of differences between the registered image pairs (Fig. 8) have been computed Eq. (18) through a translation model and an elastic model.

\[
\text{Accuracy} = \frac{\sum_{(i,j)=(1,1)}^{(\text{length}, \text{width})} |I_1(i,j) - I_2(i,j)|}{(\text{length} \times \text{width})}.
\]

Here, length and width are the image dimensions. In the previous image pair, the accuracy by translation model is 13.6 and by elastic model is 11.5. So it can be satisfactorily established that the elastic model improves the accuracy of the registration.

Although these popular measures are not equivalent in terms of robustness and accuracy, none of them is able to cope with relative intensity changes from one image to the other. A disadvantage of these error metrics is that images that would

![Fig. 8.](image_url)

(A) Non-registered images. (B) Registered images (global translation). (C) Optical flow (translation model). (D) Registered images (translation and elastic transform). (E) Optical flow (elastic model).
Fig. 9. (A) Non-registered images. (B) Registered images (global translation). (C) Optical flow (translation model). (D) Registered images (translation and elastic transform). (E) Optical flow (elastic model).

Fig. 10. (A) Non-registered images. (B) Registered images (global translation). (C) Optical flow (translation model). (D) Registered images (translation and elastic transform). (E) Optical flow (elastic model).
qualitatively be considered to be in good registration may still have large errors due to, for example, intensity variations, or slight misalignments [38]. However, in case of our study (see Fig. 8), this error metric is valid since the information content of the two images are in close agreement with each other. The brightness variation is very weak.

3.1. Remarks

To achieve better registration results, we cumulate information gradient of the previously registered images. The reference image is always taken as this image of the cumulated gradients. We obtain a panoramic gradient image, such as that shown in Fig. 12. However, we noted that at the end of a certain number of superposition,
panoramic gradient image was noisy in nature. To correct that phenomenon, we use only the information of a few (four) images gradient previously registered images.

4. Conclusion

Because of eye movements during the angiographic acquisition, a registering stage of angiographic frames is necessary to improve the quantitative analysis of the macular degeneration. The superposition of images will allow direct comparison with the previous images, to judge the disease progression (for example, to judge progression or stability of ARMD).

However, angiographic data vary considerably in intensity (e.g., the grey levels of the blood vessels vary from dark or bright in the angiographic phases) and intensity based registration algorithms are hence unsuitable for this purpose.

Between successive image pairs, the operation of the proposed method is summarized in three steps:
- morphological vascular tree filtering,
- morphological gradient computing,
- coarse-to-fine elastic registering estimation.

We have proposed an automatic registering method at successive images in macular angiographies, that can do away with the requirement of the extraction of the features and landmarks. Our registering method begins with a pre-processing step with smoothing and edge detection by using morphological tools. Finally, we estimate successively the registering transform by global translation and elastic. We used a multi-scale iterative refinement to improve the robustness and the accuracy of the image registering mechanism. In this paper, a reliable and efficient algorithm for estimating the transformation between two image data sets of a patient, taken from the same modality over time, have been presented. In fluorescein angiograms, our elastic registration algorithm has demonstrated to be robust in the presence of time-varying illumination. In ICG angiograms, the robustness of our approach is very weak. Indeed, our algorithm has been tested for 30 fluorescein and ICG angiograms before arriving at the above mentioned conclusions. The rate of success in fluorescein angiograms is more than 90%, whereas it is approximately 30% in ICG angiograms. Our alignment algorithm, which incorporates both geometric and intensity transformation, requires approximately 30 s for 1024 x 1024 image pair on a 2 GHz processor with 1 GB memory. It may be a possibility that by combining the mutual information and the gradient information, this model will yield more robust registration. Mutual information is one of the few intensity based measures that is well suited for registration of the multimodal images.

Acknowledgments

The authors wish to thank Centre Hospitalier Intercommunal of Créteil (CHIC) for providing a large number of retinal angiographic images, and for partially supporting this work.
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