An Automatic Corneal Subbasal Nerve Registration System Using FFT and Phase Correlation Techniques for an Accurate DPN diagnosis

Shumoos Al-Fahdawi, Rami Qahwaji, Alaa S. Al-Waisy and Stan Ipsopn
School of Computing, Informatics & Media, University of Bradford.
Bradford City, UK.
sun_algold@yahoo.com, R.S.R.Qahwaji@bradford.ac.uk, king_alaa87@yahoo.com, S.S.Ipson@Bradford.ac.uk,

***Abstract*— Confocal microscopy is employed as a fast and non-invasive way to capture a sequence of images from different layers and membranes of the cornea. The captured images are used to extract useful and helpful clinical information for early diagnosis of corneal diseases such as, Diabetic Peripheral Neuropathy (DPN). In this paper, an automatic corneal subbasal nerve registration system is proposed. The main aim of the proposed system is to produce a new informative corneal image that contains structural and functional information. In addition a colour coded corneal image map is produced by overlaying a sequence of Cornea Confocal Microscopy (CCM) images that differ in their displacement, illumination, scaling, and rotation to each other. An automatic image registration method is proposed based on combining the advantages of Fast Fourier Transform (FFT) and phase correlation techniques. The proposed registration algorithm searches for the best common features between a number of sequenced CCM images in the frequency domain to produce the formative image map. In this generated image map, each colour represents the severity level of a specific clinical feature that can be used to give ophthalmologists a clear and precise representation of the extracted clinical features from each nerve in the image map. Moreover, successful implementation of the proposed system and the availability of the required datasets opens the door for other interesting ideas; for instance, it can be used to give ophthalmologists a summarized and objective description about a diabetic patient's health status using a sequence of CCM images that have been captured from different imaging devices and/or at different times.**

Keywords— Diabetic, Diabetic Peripheral Neuropathy, Image Registration, Fast Fourier Transform, Phase Correlation, Automatic Nerve Segmentation, Corneal Confocal Microscopy.

I. INTRODUCTION

Recently, numerous clinical reports have pointed out that diabetes is a significant chronic health problem for which there is no currently an effective therapy [1]. For example, in 2012, the American Diabetes Association reported that, out of 29.1 million of the total US population, about 21 million had diagnosed diabetes and 8.1 million had it but were undiagnosed. In the UK, it is estimated that by 2025, 4 million people will have this disease, whether diagnosed or undiagnosed [2], [3]. In advanced cases, it is considered a main cause for foot ulceration, damage to the peripheral nerves and lower limb amputation. For example, in 2004, approximately 71,000 non-traumatic lower limb amputations were conducted in the U.S. [4]. Moreover, Diabetic Peripheral Neuropathy (DPN) is one of the most long-term complications of diabetes and affects up to about 50% of patients [5]. Consequently, an accurate diagnostic and quantification of DPN is needed to define at-risk patients and for early diagnosis and application of new therapies. The eye is the only part of the human body in which nerves can be checked directly and non-invasively, therefore, a number of helpful clinical features can be extracted from imaged of these structures for early and accurate diagnostic of DPN. Particularly, rich nerve plexuses can be observed at the subbasal corneal epithelial layer and in the retina using CCM and optical coherence tomography, respectively [4].

In this study a sequence of corneal images captured using CCM are used. In particular, those images that contain the elongated and narrow corneal nerve fibers, which are captured from a specific corneal depth range of about 10 µm inside the subbasal epithelium layer. The cornea is the outer transparent layer, approximately 500 µm thick that covers the front of the eye. It consists of five layers: the outermost epithelium membrane, followed by the Bowman's layer, the stroma, Descemet's membrane and the innermost endothelium layer [6], as shown in Fig1. The cornea is considered one of the most sensitive tissues in the human body and is densely supplied by a complex network of sensory and nerve fibers located at the joint between Bowman's layer and the subbasal epithelium layer [7]. Recently, the analysis of corneal nerves structures has received increasing interest because these nerves have been shown to produce quite important information about corneal damage various causes such as, surgical interventions on the cornea (e.g. LASIK and PRK) [8], wearing contact lens for a long time, corneal transplantation and fungal keratitis [9],[10]. More recently, a significant link has been demonstrated between a number of clinical features extracted from these structures (e.g. nerve tortuosity and length) and the severity of diabetic neuropathy [11]. However, accurate estimation and quantification of these clinical features requires a number of informative corneal

images that have structural and functional information. Despite the accuracy of the confocal microscope, a number of problems can affect the acquisition of corneal images. Firstly, the spherical shape of the cornea, which can lead to non-uniform distribution of the lighting in different areas of the corneal layers. Secondly, eye movement during the acquisition process results in some observed artefacts such as blurring. Moreover, capturing the cornea images using different sensors and/or at different times leads to differences in their displacement.

Image registration is an essential task in image analysis in which important information is obtained by integrating two or more images of the same object taken from different sensors, different viewpoints and/or at different times to produce a new informative image [12]. Registration algorithms can be divided into four classes: correlation algorithms, FFT-based algorithms, feature-based algorithms and graph theoretic algorithms [13],[14],[15]. Medical image registration has played a significant role in the data fusion of anatomical images captured using imaging modalities, such as CT, MRI, PET and SPECT, which has increasingly improved the processes of clinical diagnosis, guiding treatment, and controlling disease progression [16]. Over the last few years, a number of practical medical image registration techniques have been proposed. For example, A. Elbita and et al. [17] proposed an automatic system to produce a 3D visualization from a sequence of 2D corneal images taken from different layers. A comparison study between speeded-up robust features (SURF) and scale invariant feature transform (SIFT) based techniques is done to evaluate their performance in overlaying a sequence of CCM images that differ in their displacement and illumination conditions. F. Scarpa and et al. [18] proposed an image registration algorithm based on normalized correlation to create a 3D model of cornea using a sequence of CCM images from epithelium to endothelium. The algorithm in [18] is affected by the large distance along the z direction and the quality of CCM images to be registered. In neither [17] or [18] is there any attempt to extract and calculate clinical features that can be used for early diagnosis of the DPN. K. Ito and et al. [19] proposed a medical image registration method using Phase-Only Correlation (POC) to overlay two dental radiograph images. The method searches for corresponding points between two dental images using POC and corrects non-linear distortion using a Thin-Plate Spline (TPS) technique. More proposed medical image registration techniques can be found in [16],[20]. In this paper, an automatic corneal subbasal nerve registration system is proposed. The main aim of the proposed system is to produce a colour coded corneal image map by overlaying a sequence of CCM images may differ in their displacement, illumination, scaling, and rotation to each other. The proposed method is based on the combining the advantages of Fast Fourier Transform (FFT) and phase correlation techniques. The proposed registration algorithm searches for the best common features between a number of sequenced CCM images in the frequency domain to produce the informative image map. In this image map, each colour represents the severity level of a specific clinical feature that can be used to give the ophthalmologist a clear representation of the extracted clinical features from each nerve in the image map.

This paper is organized as follows. The proposed methodology is discussed in Section 2. Section 3 includes descriptions of the proposed corneal nerve registration system. The experimental results are discussed in Section 4. Finally, conclusions and future research directions are stated in Section 5.

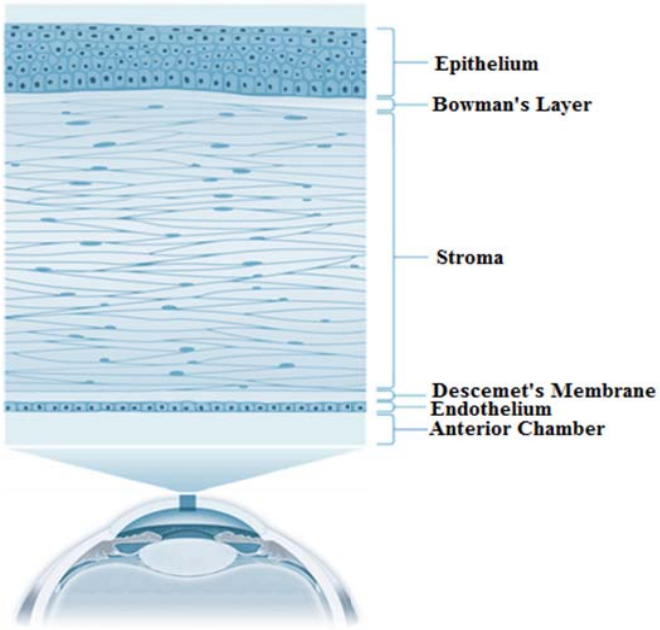

Fig.1. Corneal layers from anterior to posterior layer [21].

II. THE PROPOSED METHODOLOGY

In this section, the theoretical approach for registering two images that differ by rotation, translation and scale to each other based on the FFT properties (e.g. translation, rotation, and scaling), is explained. Image registration is an essential image processing operation, given the task to overlay two or more images and produce a more informative image than the originals [22]. In this work, the FFT is applied to the sequence of corneal sub-basal images so rotation and scaling can be detected using a phase correlation technique. This is followed by applying the transformation module for the magnitude spectrum to one of the input images, and then the output image with the second image are used to recover the translation information using the phase correlation technique in the log-polar space. The phase correlation technique is well known registration method that depends on the Fourier shift property to estimate the translation offset between two images [23]. Given two images $h_1(x,y)$ and $h_2(x,y)$ that differ by a simple translational shift x_0 in horizontal and y_0 in the vertical

directions, their corresponding Fourier transforms $H_1(u,v)$ and $H_2(u,v)$ are related as follows:

$$H_2(u,v) = e^{-j2\pi(ux_0 + vy_0)} * H_1(u,v) \quad (1)$$

Then, the normalized cross-power spectrum R between H_1 and H_2 is computed using the phase correlation technique as follows:

$$R = \frac{H_2(u,v)H_1^*(u,v)}{|H_2(u,v)H_1^*(u,v)|} = e^{-j2\pi(ux_0 + vy_0)} \quad (2)$$

Where H^* is the complex conjugate of H. The Fourier shift theorem ensures that the cross-power spectrum phase is equivalent to the difference between the two images. The translation offsets (x_0, y_0) can be acquired by detecting the location of the peak in the IFFT of R.

The FFT based phase correlation registration algorithm to detect translation, rotation, and scale differences is described in detail in [13]. If $f_s(x,y)$ is a translated, rotated and scaled replica of the reference image $f_r(x,y)$, with translation offsets (x_0, y_0), rotation angle θ_0 and scale factor k, then,

$$f_s(x,y) = f_r[k(x\cos\theta_0 - y\sin\theta_0) - x_0, k(x\sin\theta_0 - y\cos\theta_0) - y_0] \quad (3)$$

Their corresponding Fourier transforms F_s and F_r and magnitudes are defined using the Fourier shift theorem as follows:

$$F_s(u,v) = \frac{1}{k^2} e^{-j2\pi((ux_0/k)+(vy_0/k))} * F_r\left(\frac{u\cos\theta_0 - v\sin\theta_0}{k}, \frac{u\sin\theta_0 - v\cos\theta_0}{k}\right) \quad (4)$$

$$|F_s(u,v)| = \frac{1}{k^2}\left|F_r\left(\frac{u\cos\theta_0 - v\sin\theta_0}{k}, \frac{u\sin\theta_0 - v\cos\theta_0}{k}\right)\right| \quad (5)$$

Let M_s and M_r denote the magnitude spectra of f_s and f_r, respectively, they are defined as follows:

$$M_s(u,v) = \frac{1}{k^2} M_r\left(\frac{u\cos\theta_0 - v\sin\theta_0}{k}, \frac{u\sin\theta_0 - v\cos\theta_0}{k}\right) \quad (6)$$

If G_s and G_r are the transforms of M_s and M_r, expressed in polar coordinates, i.e.

$$\begin{cases} \rho = (u^2 + v^2)^{1/2} \\ \theta = \tan^{-1}(u/v) \end{cases} \quad (7)$$

then:

$$G_s(\rho,\theta) = \frac{1}{k^2} G_r(\rho/k, \theta + \theta_0) \quad (8)$$

$$G_s(\log\rho, \theta) = \frac{1}{k^2} G_r(\log\rho - \log k, \theta + \theta_0) \quad (9)$$

Next, the scaling factor k and rotation angle θ_0 are acquired using the phase correlation technique. Once, the scaling and rotation parameters are acquired, the $f_r(x,y)$ image is scaled and rotated using the obtained parameters. Finally, the phase correlation technique is applied again to find out the translation offsets (x_0, y_0). Once, all parameters (x_0, y_0, θ_0, k) have been obtained, the 2D image registration process between the two images has been completed.

III. The Proposed Corneal Nerve Registration System

The main steps of the proposed automatic corneal sub-basal nerve registration system to produce a new informative corneal image map that contains both structural and functional information are illustrated in Fig 2. The generated corneal image map can play a significant role by improving the nerve visibility and acquiring more precise clinical feature with less processing time instead of searching manually through a sequence of CCM images to extract these features from each image individually. Firstly, a sequence of corneal nerve images $(f_1, f_2, \ldots, f_n)$ are used that may differ in their displacement (viewpoint) because they are captured using different sensors and/or at different times. Moreover, they can be captured with non-uniform distribution of the lighting in different areas of the corneal layer due to the spherical shape of the cornea and may have some observed artefacts as a result of eye movement during the acquisition process. Secondly, an automatic image registration algorithm is employed to align this sequence of corneal images where the first image is aligned with the second image and the generated registered image will be aligned with the next corneal image in the sequence and so on. After that, a fully automatic nerve segmentation algorithm[1] is applied to the last generated image map from previous step. This is followed by producing a colour coded map of the corneal nerve image that represents the magnitude of the nerve tortuosity as a useful clinical feature.

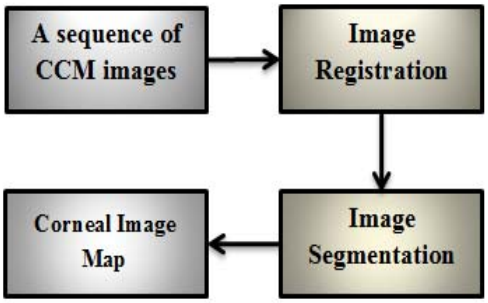

Fig. 2. The main steps of the proposed system to generate a colour coded corneal nerve image map.

A. Image Registration

The proposed registration algorithm searches for an optimal match using information in the frequency domain in order to align a sequence of corneal sub-basal images that differ in their displacement, scaling, and rotated to each others. The major steps of the implemented image registration algorithm to align two sequenced corneal images $f_1(x,y)$ and $f_2(x,y)$ can be summarized as follows:

1) Apply the 2D-FFT to the input images $f_1(x,y)$ and $f_2(x,y)$ to obtain the Fourier magnitude spectra $F_1(u,v)$ and $F_2(u,v)$, as described in (4).
2) The Fourier magnitude spectra of the input images is multiplied with a high-pass emphasis filter to reduce the noise that could be introduced by (Step 1). A simple high-pass filter is used as follows:

$$H(x,y) = (1.0 - (cos(\pi x)\, cos(\pi y)) * (2.0 - (cos(\pi x)\, cos(\pi y)) \quad (10)$$

Where, $-0.5 \leq x, y \leq 0.5$.

3) The Fourier log-magnitude spectra is used for mapping from the Cartesian coordinates to log-polar coordinates rather than the Fourier magnitude spectra, as described in (9). This conversion is known as a Mellin transform conversion.
4) In log-polar coordinates, the cross power spectrum is computed applying the phase correlation technique to both images, as described in (2). Followed by detecting the location of the peak of IFFT of the cross-power spectrum to obtain the scaling factor and rotation angle.
5) A transformed image is acquired from $f_1(x,y)$ using acquired scaling and rotation information as affine transformation parameters. In this work, the transformation is implemented using "nearest" interpolation of the $f_1(x,y)$ image. Finally, the phase correlation technique is applied again to compute the Cross power spectrum phase from the transformed image and $f_2(x,y)$ to find out the translation offsets (x_0, y_0).
6) Once, all parameters (x_0, y_0, θ_0, k) have been obtained, the image registration is performed and the generated image map is used as a reference image with the next image in the sequence of CCM images, as shown in Fig.3.

A block diagram of the image registration algorithm using the FFT based phase correlation technique, is shown in Fig.4.

B. Image Segmentation

In this paper, the nerve tracing task is performed using a fully automatic corneal sub-basal nerve segmentation system. This system is still unpublished work and it consists of two main stages: the nerve segmentation and a morphometric parameters quantification stage. The nerve segmentation stage consists of three steps: preprocessing, morphological operations and edge detection step. In the morphometric parameters quantification stage, a number of clinically useful features are calculated including length, thickness, tortuosity of nerve that can be used for the early diagnosis and follow up of DPN using CCM images. The performance of the nerve segmentation system has been tested and evaluated on a dataset consisting of 498 cornea sub-basal nerve images and results obtained have demonstrated the efficiency of the proposed system. Fig.5 shows some examples of applying the nerve segmentation system on the generated corneal image map.

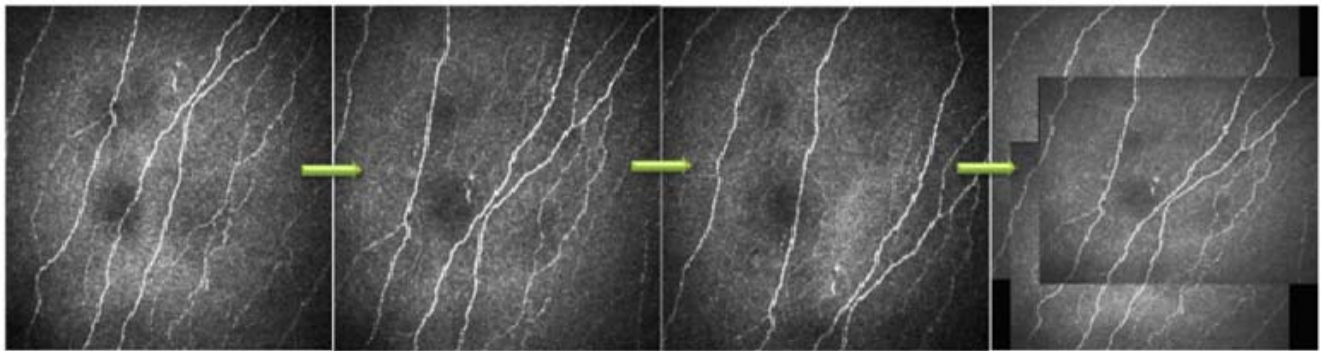

Fig.3. Applying the image registration algorithm on three sequenced CCM images where the last column represents the output.

[1] Shumoos Al-Fahdawi and et al, "*A Fully Automatic Nerves Segmentation and Morphometric Parameters Quantification System for Early Diagnosis of Diabetic Neuropathy in Corneal Images* ", Unpublished working paper, 2015.

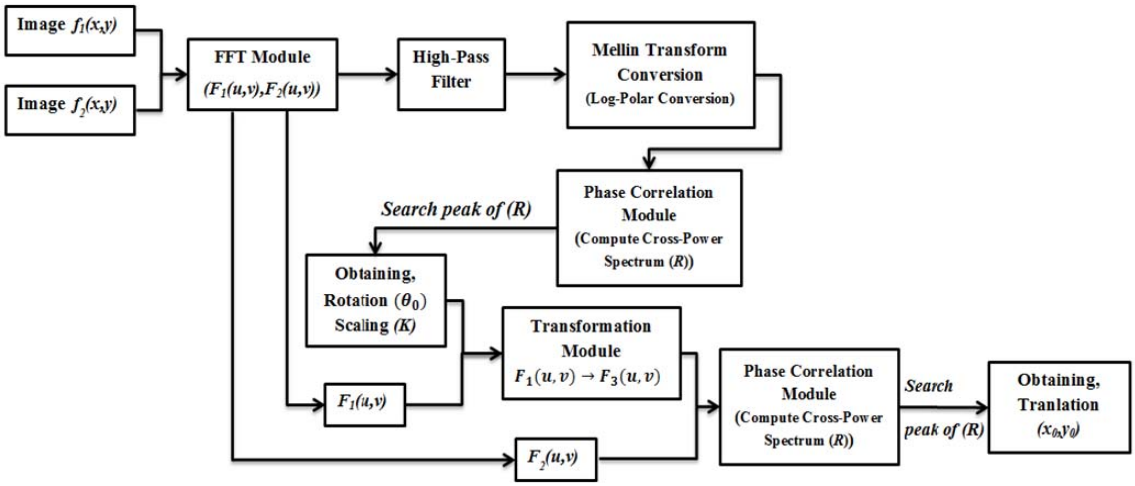

Fig.4. Overview of the automatic Fourier and phase correlation based image registration algorithm.

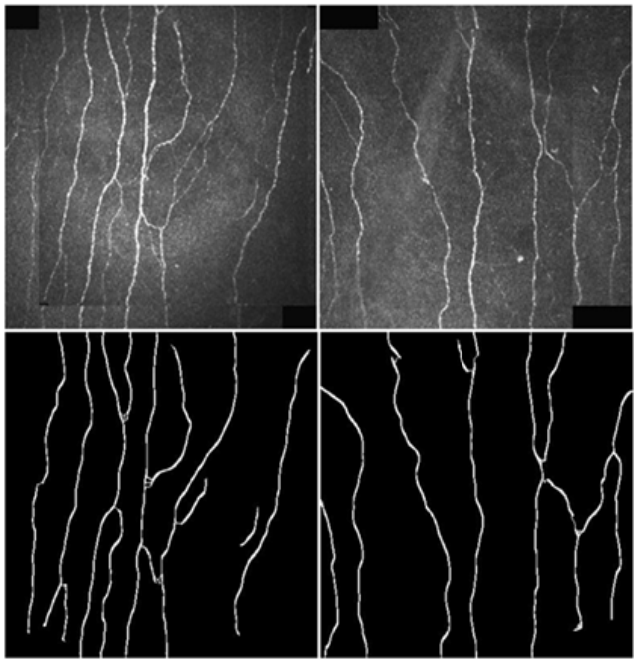

Fig.5. Corneal nerve segmentation system outputs: (Top) row is the original corneal images and (Bottom) row is binary segmented images.

C. Corneal Image Map

The final output of the proposed system produces a colour coded corneal nerve image map that can be used to give ophthalmologists an efficient and clear representation of the extracted clinical features from each nerve in the image, for example a specific colour can refer to the severity level of a specific clinical feature (e.g., tortuosity), as shown in Fig.6.

IV. EXPERIMENTAL RESULTS

Due to unavailability of a dataset that contains a large sequence of CCM images for each subject, the performance of the proposed system is evaluated and tested on a dataset of 30 subjects (18 controls and 12 diabetic patients) with a sequence of CCM images that varies between 3 and 4 images per subject. In this dataset, the CCM images were captured using a Heidelberg Retinal Tomograph equipped with a Cornea Rostock Module (HRT-CRM: Heidelberg Engineering, Heidelberg, Germany). The images are stored in JPEG format with a size of (384×384) pixels covering (400×400) μm^2 of the cornea at an optical magnification of 63X. In this work, the severity of the nerve tortuosity as a useful clinical feature is calculated and presented as a colour coded map, where the red coloured nerves refer to the highest level of the nerve tortuosity while the green coloured nerves refer to the lowest or normal level of the nerve tortuosity, as shown in Fig.6. The severity of the nerve tortuosity is determined using an empirical threshold which is defined after extensive experiments on another dataset consists of 20 subjects with a number of images varies between 12 and 38 images per subject. In this dataset, 8 subjects are non-diabetic and 12 are diabetic patients. The results obtained have demonstrated the reliability and efficiency of the proposed registration technique in completing the structure of the nerve and producing a new informative image map that can be used in a successful diagnostic system. In addition to ability of the proposed system in tracing all nerves of the generated map in real-time, where the execution time starting from image registration stage to generating the colour coded map is about 10 seconds. The execution time without image registration is about 8.8 seconds, which means for three CCM images it takes about 26.4 seconds. This means the execution time has been reduced by more than half to analyse a more informative CCM image. These times were measured by implementing the proposed system on a PC with the Windows 8.1 OS, 6 GB of RAM and a 1.80 GHz Core i5-3337U CPU. The system code was written to operate in MATLAB R2010a. In addition, The Average Nerve Tortuosity (ANT) and the Average Nerve Length (ANL) are calculated by deriving the average from the generated map for each subject in the dataset. As shown in Fig.7 one can see that the nerve tortuosity is higher in the

diabetic patients group than in the controls group. While, the nerve length is lower in the diabetic patients group.

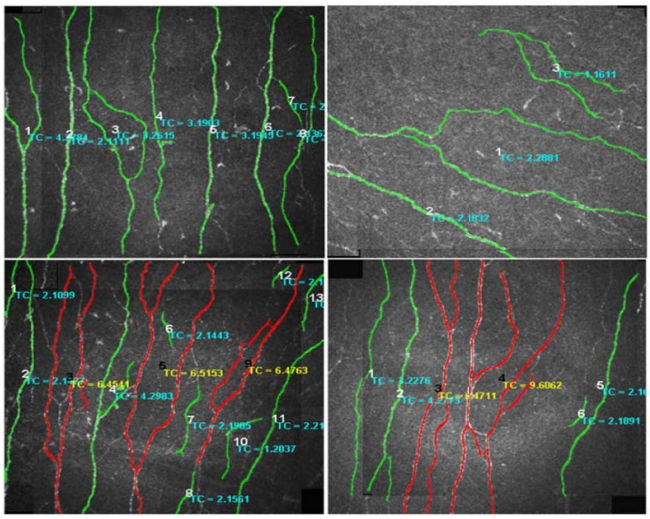

Fig.6. The colour coded corneal nerve image map: top row represents the control group, while the bottom row represents the patients group.

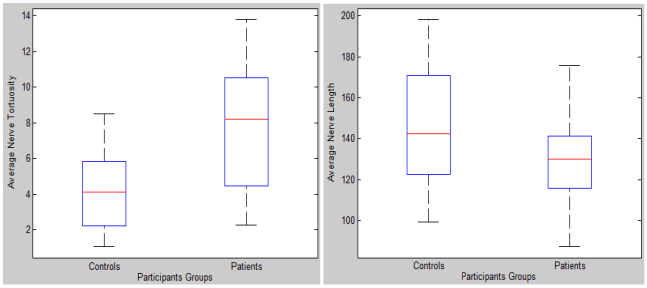

Fig.7. Representative box-plots illustrating: (a) ANT and (b) ANL.

V. CONCLUSIONS AND FUTURE WORK

In this paper, an automatic corneal subbasal nerve registration system is proposed using a Fast Fourier Transform (FFT) based phase correlation technique. The main part of the proposed system is the image registration method that based on finding the best common features between a number of sequenced CCM images in order to produce a more informative corneal image than the original images. In addition the system produces a colour coded corneal image map to help ophthalmologists produce faster and more accurate diagnoses. In this paper, the severity of nerve tortuosity as useful clinical feature is represented using different colour codes. The results obtained have demonstrated the reliability and efficiency of the proposed system to trace all nerves of the generated map with shorter time compared with tracing nerves in all the original images. Moreover, the efficiency of using the last generated image map has been investigated by calculating the ANT and ANL in order to distinguish between the healths of different patient groups. The future research directions include: improving the registration accuracy; applying the proposed system on large dataset that contains a higher number of sequenced of CCM images; demonstrating the efficiency of the generated image map in providing other useful clinical features such as the nerve thickness and density.

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