Corneal Confocal Microscopy Image Quality Analysis and Validity Assessment

M.A. Dabbah[1]
m.a.dabbah@manchester.ac.uk
J. Graham[1]
jim.graham@manchester.ac.uk
R.A. Malik[2]
rayaz.a.malik@manchester.ac.uk

[1] Imaging Sciences and Biomedical Engineering (ISBE)
The University of Manchester
Oxford Rd, Manchester, M13 9PT, UK

[2] Cardiovascular Research Group
The University of Manchester
Grafton St., Manchester, M13 9NT, UK

Abstract

Corneal Confocal Microscopy (CCM) image analysis is a new non-invasive and iterative surrogate endpoint to detect, monitor and quantify Diabetic Peripheral Neuropathy (DPN). This paper presents an automated system that analyses CCM images and assesses their quality for further analysis and quantification. The method is based on a dual-model nerve-fibre detection technique followed by an SVM linear classifier, which uses the area distribution of the response image. A Monte-Carlo analysis has shown a correct recognition rate of 92% on a database of images captured randomly from the cornea at different confocal depths.

1 Introduction

The accurate detection, quantification and monitoring of Diabetic Peripheral Neuropathy (DPN) are important to define at-risk patients, anticipate deterioration, and assess new therapies. DPN is one of the commonest long-term complications of diabetes and current methods of detecting and quantifying it lack sensitivity, require expert assessment and focus only on large fibres (neurophysiology) or are invasive (skin/nerve biopsy).

Corneal Confocal Microscopy (CCM) allows nerve-fibres to be visualised in the Bowman's membrane near the surface of the cornea. Recent research [4, 5, 7] has shown that using CCM, DPN can be accurately quantified through corneal nerve-fibre morphology. CCM is a non-invasive and a reiterative test that might be an ideal surrogate endpoint for DPN. The measurements reflect the severity of DPN and relate to the extent of intra-epidermal nerve-fibre loss seen in skin biopsy.

One of the major advances of CCM is the rapid ($\approx 2_{min}$) acquisition of images of small nerve-fibres in patients. However, analysis of CCM images using interactive manual image analysis tools is highly labour-intensive and requires considerable expertise to quantify nerve-fibre pathology. Therefore, in order to extend this technique to a wider clinical practice and to be clinically useful as a diagnostic tool, it is essential that the measurements are extracted automatically.

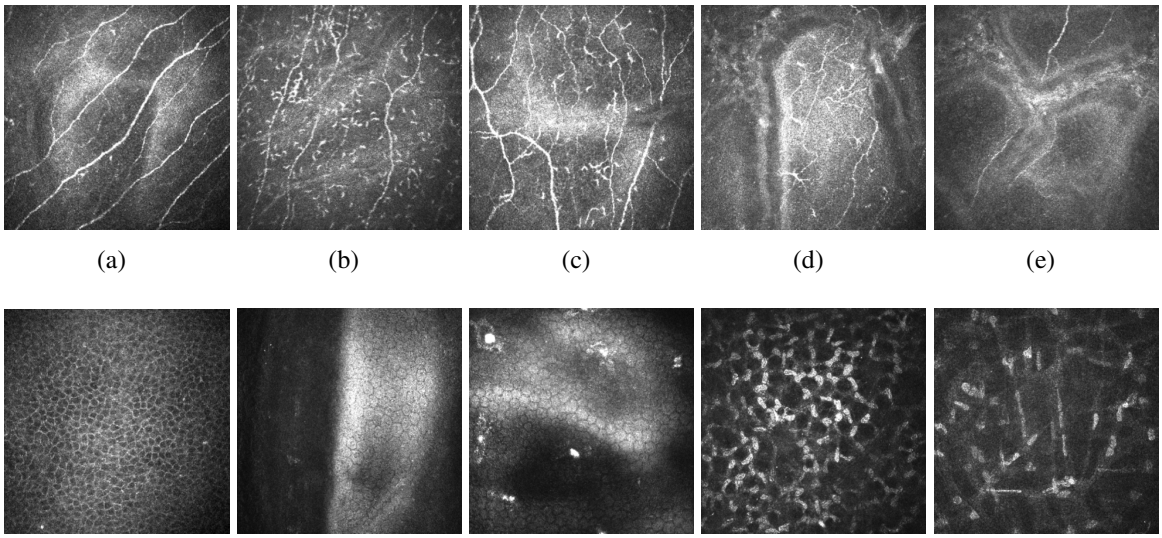


Figure 1: Samples of CCM images captured by the HRT-III microscope at different depths. The images in the top row are considered to be valid for nerve-fibre detection while the images in the bottom row are not.

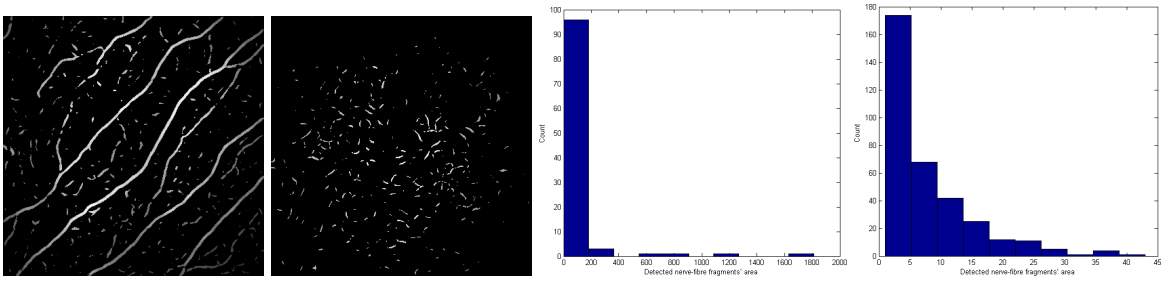
An important stage in the analysis of CCM images (sample images are shown in Figure 1) is the detection of nerve-fibres. A heuristic approach [8], using a method previously applied to detecting blood-vessels in retinal images, has been used for detecting nerve-fibres in CCM images. A comparison of methods for enhancing contrast of nerve-fibres in analysis of CCM images showed that the use of a Gabor wavelet that is oriented along the locally prominent nerve-fibre direction gave superior performance to a well-established linear structure detector [1].

Figure 1 shows a number of CCM images, some of which show nerve-fibres, having been collected from the Bowman's membrane. In others, the plane of focus is in the stroma, where no nerve-fibres are present. Fully automated analysis requires a method for identifying images that are valid for analysis. In this paper we present a method to validate the quality and the usability of CCM images. In Section (2) we briefly introduce our dual-model nerve-fibre detection algorithm [2]. The validity assessment of CCM images is described and discussed in Section (3). Finally, Section (4) concludes the findings.

2 The Dual-Model Nerve-fibre Detection Algorithm

In this section we briefly describe a dual-model detection algorithm [2], which we have designed to automatically enhance contrast and detect nerve-fibres. The nerve fibres in CCM images often appear with low contrast against a sometimes noisy background (Figure 1). The algorithm comprises two separate models, one for the background and another for the foreground (nerve-fibres), which work interactively. Using a 2D Gabor wavelet and a Gaussian envelope, the dual-model of foreground (nerve-fibres) and background are constructed and applied to the original CCM image. Since the images exhibit local directionality over a range of scales, the detection relies on estimating the correct local and dominant orientation of the nerve-fibres.

Identifying low-contrast fibrous structures is a commonly encountered problem in a number of applications. Our dual-model was evaluated in comparison with some established



(a) (b) (c) (d)

Figure 2: Illustration of area distribution dissimilarity. (a) and (b) detection responses of the images in Figure 1(a) and 1(f) respectively. (c) and (d) are their area distributions.

methods used to address this problem and the results showed an improved performance, suggesting that the dual-model may be an appropriate contrast enhancement method in other application domains. In [2] we show that automatic detection of nerve-fibres using this method gives equivalent results to manual analysis. Unlike other, more general feature detection approaches, such as the Dual-Tree Complex Wavelet Transform (DTCWT) [6] or the Monogenic signal [3], this algorithm [2] does not assume uniform error on the input images, therefore it tries to estimate local error distribution for each processed image. We have shown this to have a significant effect on the final performance of the system [2].

3 CCM Validity Assessment

3.1 Experimental Settings and Database

The evaluation is conducted on a database of 415 CCM images captured using the HRT-III microscope[1] from 59 subjects (5 controls and 54 diabetic patients). The images have a size of 384×384 pixels, 8-bit grey levels and are stored in BMP format. The resolution is $1.0417 \mu m$ and the field of view is $400 \times 400 \mu m^2$ of the cornea. For each individual, several fields of view are selected manually from the cornea at different depths and locations. Images from near the centre of the cornea that show recognisable nerve-fibres are considered to be valid (Figure 1). The validity ground-truth of images is assigned manually and then used to evaluate the performance of the system. There are 255 valid CCM images *i.e.* 61.45% of the database.

3.2 Classification using Detected Nerve-fibre Area Distributions

In order to assess the validity of each CCM image, the dual-model detection algorithm is applied to the images. Then, in the response images, genuine nerve-fibres exhibit longer and better connected linear structures whereas noise and other cells are usually represented as disoriented and smaller fragments as shown in Figure 2. Therefore, each response image is quantified as a histogram that represents the area distribution of the detected features in the response image. For example, Figure 2(c) shows the histogram of the area distribution of the detected nerve-fibres in a valid CCM image, while Figure 2(d) corresponds to a invalid CCM image. It is clear that for a valid image there are smaller number of fragments and there are

[1] The Heidelberg Retina Tomograph (HRT-III) confocal scanning laser ophthalmoscope developed by Heidelberg Engineering Inc. The instrument can be converted into a confocal corneal microscope using a microscope lens which is attached to the standard lens.

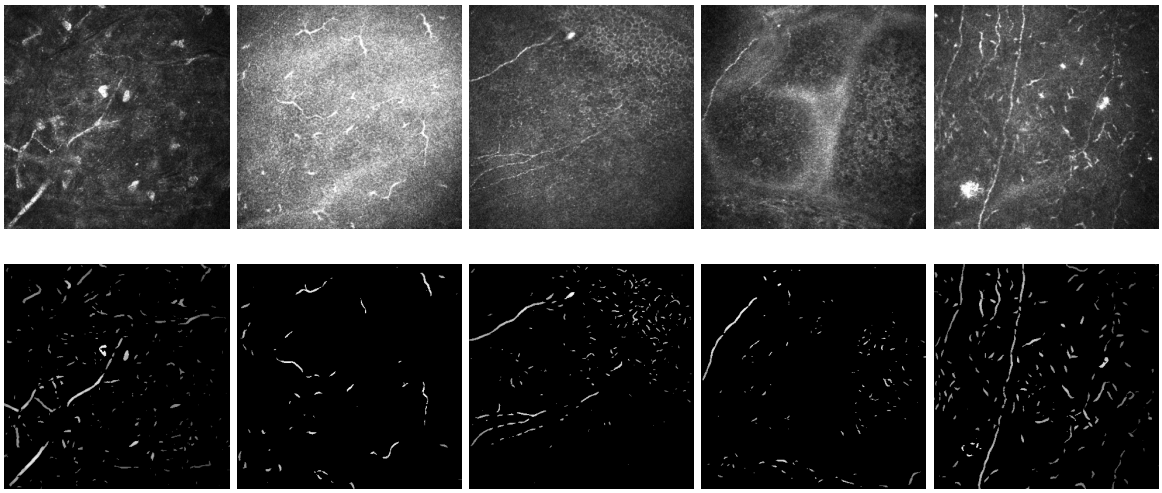
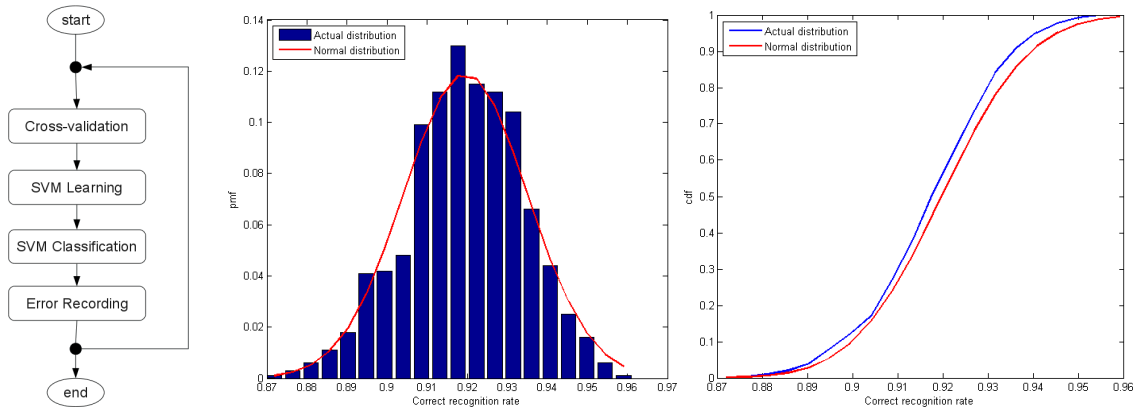


Figure 3: The dual-model detection response images in the bottom row correspond to the original images in the top row. The first image from the top-left is an example of false positive misclassifications; the rest are examples of false negative misclassifications.



(a) (b) (c)

Figure 4: Monte-Carlo simulation. (a) the flow chart of the Monte-Carlo simulation, (b) the *pmf* of the correct recognition rate and (c) its *cdf*.

several large connected linear structures, which do not usually exist in invalid images. Hence we use these histograms as input vectors to a linear SVM classifier in order to distinguish valid and invalid images.

3.3 Monte-Carlo Simulation

The validity assessment experiment was conducted on the same database described in Section 3.1. In order to generalise the outcome, a Monte-Carlo simulation is carried out using hold-out cross-validation as shown in Figure 4(a).

We used a linear SVM classifier, although clearly other classifiers can be considered. As illustrated in Figure 4(b), the *pmf* of the correct recognition rate in splitting the two groups has the mean $\mu = 0.9196$, the median $\mu_{1/2} = 0.9179$ and the standard deviation $\sigma = 0.0155$. Figure 4(b) shows that the *pmf* of the correct recognition rate can be approximated to a normal distribution. However the *pmf* is slightly narrower than the normal distribution as indicated by the steeper *cdf* in Figure 4(c). According to the *cdf*, 73% of the classifications lie within the first confidence interval, $cdf(\mu+\sigma) - cdf(\mu-\sigma) = 0.73$, which is higher than

the normal distribution's error function $erf\left(\frac{n}{\sqrt{2}}\right) = 0.682$ when $n = 1$, which demonstrates stability and robustness. The full analysis takes about 5 seconds in order to classify a single CCM image.

Figure 3 shows examples of the misclassification error. Most of these images are considered valid; however, they do not contain much information to extract. On the other hand, some linear structures appear in invalid images, which causes a misclassification.

4 Conclusion

CCM imaging is a promising alternative modality with the potential to radically change the diagnosis and assessment of DPN. This paper address the quality and validity assessment of CCM images before they are considered for further analysis or diagnosis. The paper has shown the robustness of the dual-model detection algorithm with respect to the dynamic input image set. Using the Monte-Carlo simulation of a linear SVM classifier on the features extracted by the detection algorithm, we have demonstrated that the system is robust and can correctly classify 92% of valid and invalid images.

References

[1] M. A. Dabbah, J. Graham, M. Tavakoli, Y. Petropoulos, and R. A. Malik. Nerve fibre extraction in confocal corneal microscopy images for human diabetic neuropathy detection using gabor filters. In *Medical Image Understanding and Analysis (MIUA)*, pages 254–258, July 2009.

[2] M. A. Dabbah, J. Graham, M. Tavakoli, Y. Petropoulos, and R. A. Malik. Dual-model automatic detection of nerve-fibres in corneal confocal microscopy images. *The International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI), In Press*, 2010.

[3] M. Felsberg and G. Sommer. The monogenic signal. *IEEE Transactions on Signal Processing*, 49(12):3136–3144, Dec 2001.

[4] Parwez Hossain, Arun Sachdev, and Rayaz A Malik. Early detection of diabetic peripheral neuropathy with corneal confocal microscopy. *The Lancet*, 366(9494):1340–1343, 2005.

[5] P Kallinikos, M Berbanu, C O'Donnell, AJM Boulton, N Efron, and RA Malik. Corneal nerve tortuosity in diabetic patients with neuropathy. *Investigative Ophthalmology & Visual Science*, 45(2):418–422, Feb. 2004.

[6] Nick Kingsbury. Complex wavelets for shift invariant analysis and filtering of signals. *Applied and Computational Harmonic Analysis*, 10(3):234 – 253, 2001.

[7] R A Malik, P Kallinikos, C A Abbott, C H M van Schie, P Morgan, N Efron, and A J M Boulton. Corneal confocal microscopy: a non-invasive surrogate of nerve fibre damage and repair in diabetic patients. *Diabetologia*, 46(5):683–688, 2003.

[8] A. Ruggeri, F. Scarpa, and E. Grisan. Analysis of corneal images for the recognition of nerve structures. In *IEEE Conference of the Engineering in Medicine and Biology Society (EMBS)*, pages 4739–4742, Sep. 2006.