A Review of Computerised Nailfold Capillaroscopy

Niraj Doshi[1]
N.Doshi@lboro.ac.uk
Gerald Schaefer[1]
gerald.schaefer@ieee.org
Kevin Howell[2]
k.howell@ucl.ac.uk

[1] Department of Computer Science
Loughborough University
Loughborough, U.K.

[2] Department of Rheumatology
Royal Free Hospital
London, U.K.

Abstract

Nailfold capillaroscopy (NC) is a valuable method for observing micro blood vessel characteristics and is particularly useful for early detection of scleroderma spectrum disorders and evaluation of Raynaud's phenomenon. Diagnosis involves the recognition of *early*, *active* and *late* patterns, also known as NC patterns or scleroderma (SD) patterns, in the captured NC images/image sequences. NC assessment is typically performed by manual inspection, which is subjective, requires extensive experience, and is a time consuming task. Computerised automation can help to address these problems, yet relatively little work is reported in the literature on such approaches. In this paper, we present a review of work in computerised nailfold capillaroscopy. We discuss semi-automatic, image and video based NC techniques, and in particular image enhancement methods, capillary extraction algorithms and parameter measurement methods.

1 Introduction

Nailfold capillaroscopy (NC) is a non-invasive imaging technique employed to assess the condition and morphology of capillaries in the nailfold. It is recognised as a reliable method for observing micro blood vessel characteristics and as a standard method for diagnosing diseases such as systemic sclerosis (SSc) [12], Raynaud's phenomenon [5], and other connective tissue diseases such as dermatomyositis, antiphospholipid syndrome [7], and Sjögren's syndrome [30] which lead to morphological alterations of capillaries. Specific NC patterns in SSc have been described in [21], and were later refined into early, active and late patterns in [4].

Nailfold capillaroscopy is performed by observing capillaries in the nailfold area under a microscope. A digital camera attached to the microscope enables the capillaries to be viewed and recorded. Morphological features that are indicative in NC images include enlarged and giant capillaries, haemorrhages (microbleeding), loss of capillaries, disorganisation of the vascular array, and ramified/bushy capillaries [6].

NC assessment is typically performed by manual inspection, which is subjective, requires extensive experience, and is a time consuming task. Even for manual measurement of capillaroscopy parameters, there is a demand for better image quality. For example, a projection

method for measuring capillaroscopic parameters was proposed in [18], where (negatives of) capillary images were projected on tracing paper at 120x magnification for manual tracing of the capillary outlines.

An accurate extraction of capillary information from the images becomes challenging due to image noise, dust on lenses, micro-motion of fingers and air bubbles in the immersion oil. Maybe because of these difficulties, relatively little work has been reported on computerised NC image analysis.

Computerised NC techniques should help to address some of these issues. The employed algorithms generally involve image enhancement, capillary extraction and capillary parameter measurements. In the remainder of the paper, we discuss these steps for semi-automatic, image based and video based approaches.

2 Nailfold Capillaroscopy

Capillaroscopy is an established technique to investigate micro-vascular involvement in various diseases. Examination of capillaries for finding a relation between conjunctival inflammation and the presence of an inextricable knot of capillary loops was noted by Italian physician Giovanni Rasori around 200 years ago using a magnifying glass [5]. In 1911, Lombard discovered that human skin capillaries can be observed using a microscope after the application of a drop of immersion oil. Further to this, Weiss in 1916, was able to take a picture of capillaries using a primordial camera. In 1925, Brown and O'Leary have shown the use of capillaroscopy for observing capillary abnormalities in Raynaud's phenomenon (RP) characterised by Systemic Sclerosis (SSc). Nevertheless, capillaroscopy was then mostly neglected for several decades until, in 1973, Maricq and LeRoy published the first paper describing specific capillaroscopic patterns in SSc [21].

Following this, in a resurge of interest, various works on capillaroscopic patterns, emphasising mainly the relations between capillary patterns and particular diseases, were published. At the same time, capillaroscopic image acquisition techniques and protocols improved significantly. For acclimatisation, the subject is typically kept in the procedure room for a minimum of 15 minutes, and the room temperature kept between 20 and 22 °C. The nailfolds of several fingers are examined, and a drop of immersion oil used to improve the image resolution [6]. Observation can be conducted using various instruments including ophthalmoscopes, stereomicroscopes, photomicrography and video-capillaroscopy systems. Dermoscopic instruments have also been used successfully for NC evaluation [14], however the produced images are of lower contrast.

Morphological anomalies of nailfold capillaries are indicators of an underlying connective tissue disease or a scleroderma spectrum disorder. In [3], the need for capillaroscopy in rheumatology for diagnosis of diseases is discussed. There are various situations where capillaroscopy can prove to be effective and useful, including:

- First-line examination of patients with RP: in RP patients, even a single morphological abnormality may alert the physician to the possibility of secondary RP.
- Transition from primary RP to secondary RP: it is suggested that patients with primary RP undergo capillaroscopic analysis every 6 months to detect a possible transition to secondary RP to early SSc [19].
- Differential diagnosis of scleroderma related conditions: (a) SSc, dermatomyositis and mixed connective tissue diseases; (b) primary Sjögren's syndrome.

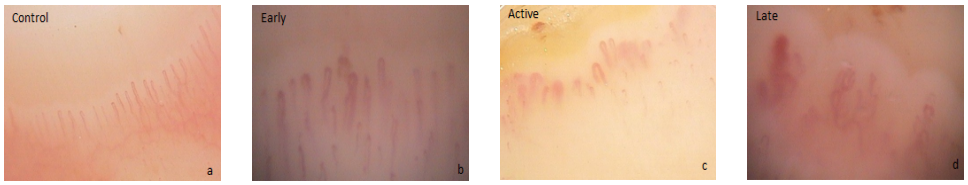

Figure 1: Sample SD patterns: (a) healthy patient, (b) early, (c) active, (d) late SD pattern.

- Early detection of severe microangiopathy in SSc, which can lead to digital ulceration and necrosis.
- Therapy monitoring: visualisation of a single loop image can be helpful for therapy monitoring.
- Assessment of microvascular involvement in other autoimmune rheumatic disorders: systemic lupus erythematosus, psoriatic plaques.

Diagnosis of the above conditions is carried out by evaluating capillary morphology. In healthy subjects, the observed pattern can be characterised by [12]:

- cutaneous capillaries at the nailfold are parallel to the skin surface, and their general configuration is hairpin or u-shaped;
- uniform distribution of capillaries, although isolated morphological abnormalities may be present;
- the number of capillaries in the distal row is 9 to 13 capillaries per mm;
- the diameter of the erythrocyte column ranges between 6.2 and 19 μm at the arteriolar limb and between 8 and 20 μm at the venular limb;

and remain unchanged for many years.

The most important disease encountered underlying RP is systemic sclerosis (SSc) or scleroderma. SSc is characterised by progressive skin and visceral organ fibrosis. Early diagnosis of scleroderma is only possible by examination of nailfold capillaries [3]. Researchers have observed that 90% of patients with scleroderma show a typical NC pattern called scleroderma pattern or SD pattern. However, similar patterns are also observed in other closely related disorders such as dermatomyositis, and mixed connective tissue diseases. Typical SD patterns show enlargement of capillary loops, loss of capillaries, disruption of the capillary bed and distortion and budding of capillaries.

The degree of these abnormalities gives an indication of the severity and progression of diseases, and allows the classification into three SD patterns [4]:

- *Early:* few giant capillaries, few capillary haemorrhages, relatively well preserved capillary distribution, no evident loss of capillaries.
- *Active:* frequent giant capillaries, frequent capillary haemorrhages, moderate loss of capillaries with some avascular areas, mild disorganisation of the capillary architecture, absent or some ramified capillaries.
- *Late:* irregular enlargement of the capillaries, few or absent giant capillaries, absence of haemorrhages, severe loss of capillaries with large avascular areas, severe disorganisation of the normal capillary array, frequent ramified/bushy capillaries.

These patterns are also used as reference patterns to evaluate other rheumatic diseases. An SD capillary pattern is often present in dermatositis/polymyositis. Also, the presence of a scleroderma capillary pattern among patients with Raynaud's syndrome and undifferentiated connective tissue disease is observed [23]. An abnormality in capillary length, capillary width, and apical length and width is significant in patients who developed SSc.

3 Semi-automatic NC analysis

Earlier NC automation systems required user interaction, with the majority of proposed semi-automatic algorithms being dedicated to image enhancement and capillary extraction. In [29], low contrast in NC images is addressed by producing a hand drawing, which is performed using a magnifying projector and measurements are conducted in an area of 3×3 mm, centred with respect to the midpoint of the hand-drawing. The Leitz Quantimet 570 c image analysis system was used for image evaluation.

Clearly, drawing/tracing is a time consuming task and dependent on the individual's skill. In [17], an image processing application (Adobe Photoshop) was used for colour filtering and grid display to measure lengths and other capillary parameters. Photoshop can also be used for image enhancement but was not suitable for the automatic capillary parameter extraction.

In [22], an NC image is filtered by a low pass filter and subtracted from the original image to remove lightning variations. Then, a threshold is applied to obtain a binary image of capillaries and connectivity analysis is performed to reduce the noise in the image. Based on a user defined region of interest, measurements are then taken for capillaries inside the selected area. The employed image enhancement was found to be able to minimise various types of noise present in the images. It was observed that computer aided analysis had low inter-observer variability and provided a quantitative and sensitive method of assessing capillary abnormalities.

In [15], captured NC images are enhanced by a simple transform where image contrast is stretched based on the minimum and maximum intensity values. The user defines several regions of interest (ROIs) which are then digitally magnified using interpolation. After preprocessing, each ROI is marked as capillary or non-capillary by the user. Finally, gradient information is used for capillary edge detection and a skeleton is extracted to measure the various capillary parameters. This skeleton is divided into the venous limb, transitional segment (loop of capillary) and arterial limb. Tortuosity is calculated as the ratio of skeleton length to the shortest distance between the skeleton end points. Local limb diameters for various points across the skeleton are calculated, and a final limb diameter is reported as the average over these.

More recently, a semi-automatic method for capillary vessel tracking was suggested that makes use of a non-directional graph technique for capillary extraction [27]. First, a point on the capillary is located manually, and then the algorithm seeks for neighbouring points, until the whole vessel is extracted. One seed point per capillary is taken as an input for graph construction, although it is possible to select more than one point per capillary. For each point, model identification is performed and based on the selected model a set of neighbour vertices generated.

4 NC image analysis

In general, image based algorithms are focussed on image enhancement, capillary extraction and capillary parameter measurement. An edge preserving smoothing and contrast enhancing filter was shown to be suitable for subsequent image analysis algorithms in [8] where various filters were applied on NC images and their edge preserving and noise removing ability were examined. In [11], bilateral filter and enhancer algorithms were found to lead to better NC image quality compared to various other techniques. Nevertheless, even the best techniques were found to be insufficient to deal with very poor quality images and with

motion artefacts.

Image enhancement is typically followed by capillary extraction which is important for measuring of capillary size and characterising its shape. Region growing based on predefined conditions is widely used for this purpose. A set of conditions is checked for neighbouring pixels and those neighbours that meet the conditions included in the capillary region. Often, prior to capillary extraction, the image is binarised using thresholding and the binarised images analysed in an iterative skeletonisation procedure [31, 32].

The results depend on the binarisation quality and are confounded by noise and image quality. A Markov chain based edge detector may lead to improved performance as was suggested in [13] where the authors argued that classical edge detectors are insufficient as intensity changes continuously perpendicular to the capillaries. Consequently, a second order derivative and the relation between pixel locations is used to search for the centre line of vessels.

In [10], following image enhancement using bilateral enhancer, and prior to a capillary skeleton extraction algorithm, the image is processed by a difference of Gaussian filter (DoG) which addresses the problem of varying illumination and non-uniform background.

After extraction, capillary parameters are measured in a final step. A very simple approach for thickness analysis is to directly measure the thickness from the image [31, 32]. After vessel skeletonisation, the distance from the border to the median is used to evaluate enlarged or giant capillaries. A somewhat more complex approach is described in [24]. Here, for each point of the skeleton image, thickness and curvature are calculated. Thickness estimation is performed in pixel units whereas arc-chord ratio is used for curvature estimation. A feature vector for the purpose of classification is created from the data obtained by capillary analysis. An extension to thickness analysis is proposed in [16], where a cuticular class is developed to consider the length and width of capillaries. The area is determined by calculating the number of pixels contained within the capillary, while capillary length is calculated by segmenting the image from base to tip and then counting the segments. The mean capillary width is then calculated by the ratio of area and length.

Tortuosity analysis is carried out on whole vessels and not on the single curves connected to each other, and describes how twisted a capillary is, how many turns it has etc. A simple approach is presented in [16], where the change in gradient over a limb is considered to calculate the tortuosity. If the tortuosity angle is greater than a threshold, then the capillary is classified as tortuous. A more complex method for tortuosity measurement of nailfold capillaries is proposed in [26] and returns a single numerical value which represents the tortuosity of a vessel. Non-directed and directed graph analysis, curvature sign calculation and arch-cord ratio is employed to derive the tortuosity index.

An approach for avascular area detection in NC images is presented in [25]. Histogram analysis and classification techniques are employed, and after enhancement each image is cut into horizontal slices of constant width. Vertical projection is then used for each slice of an image; since capillaries appear dark in the image, local minima in the projection are considered the capillary centre and this centre is used to find local maxima.

In all of the above approaches, individual capillaries are extracted and analysed. In [24, 31, 32], a classifier is used to characterise capillaries based on their properties. The parameters for all capillaries in the image are then considered to classify image into *control*, *early*, *active* or *late* groups.

In [9, 28], a holistic approach NC pattern identification is suggested. It is shown that, using global texture analysis and with appropriate training of a classifier, SD patterns can be recognised without having to extract individual capillaries.

5 NC video analysis

Video NC can overcome motion artefacts and poor contrast of NC images. In [22], an enhancement algorithm and the use of lens filters as auxiliary filtering device are proposed. Initially, 100 frames are averaged, filtered with a low pass filter and the filtered image then subtracted from its original to remove lightning heterogeneity. To correct motion artefacts, a linear feature detector is employed coupled with a Hough transform [2]. Here, the linear feature detector gives a skeletal image which is processed by the Hough transform to calculate the transformation between two points in successive images.

Averaging of images is one of the main approaches suggested for noise suppression and estimation of motion artefacts. Supplementary to this, averaging is also useful to address the problem of temporal variability in capillaroscopic images [1]. At single snapshots, transparent capillaries may look incomplete due to gaps in the flow of blood cells. Hence, the complete vessel can be integrated from a sequence of successive video frames. It is observed that combining the information from a video frame sequence by subtracting a multiple of the standard deviation from the mean value for each pixel gives good results.

More recently, a local histogram equalisation and thresholding based approach for video capillaroscopy is suggested in [20]. The green channel is processed by local and global histogram equalisation methods in order to enhance the contrast between background and capillaries. Thresholding is then performed on both globally equalised and locally equalised images to produce a binary image that separates capillaries from the background. Globally thresholded images preserve the major non-capillary area while local thresholding allows for precise segmentation of capillaries. These images are then combined, while information from multiple frames is combined to build a final binary image. A morphological (erosion-based) algorithm is iteratively applied to thin the capillaries and extract their skeletons.

6 Conclusions

Nailfold capillaroscopy is a useful tool for the evaluation of scleroderma, Raynaud's phenomenon and other rheumatic diseases which lead to changes in capillary shape, organisation and density. In this paper, we have summarised the literature on computer algorithms which are used for NC image analysis. In general, NC automation algorithms start with an image enhancement procedure followed by capillary extraction and parameter measurement. The extraction step involves a skeletonisation algorithm or walking algorithm to extract capillaries. Video based NC can give better image quality by exploiting temporal information and redundancy for subsequent image analysis. Capillary length, tortuosity, thickness and avascular area measurements are employed for identifying scleroderma patterns in NC images. With recent development in computer algorithms, user interaction is not required for NC image analysis and algorithms are able to overcome noise and contrast related issues. Furthermore, automation of parameter measurement may reduce errors in diagnosis. The field of NC image analysis is a relatively young one, and consequently there is still much scope for further research. In particular, more robust algorithms are required which are capable of coping with the large range of image quality encountered in nailfold capillaroscopy.

References

[1] P. D. Allen, C. J. Taylor, A. L. Herrick, and T. Moore. Enhancement of temporally variable features in nailfold capillary patterns. In *British Machine Vision Conference*, volume 2, pages 535–544, 1998.

[2] P. D. Allen, C. J. Taylor, A. L. Herrick, and T. Moore. Image analysis of nailfold capillary patterns from video sequences. In *Medical Image Computing and Computer-Assisted Intervention*, volume 1679, pages 698–705, 1999.

[3] R. D. Angelis, W. Grassi, and M. Cutolo. A growing need for capillaroscopy in rheumatology. *Arthritis and Rheumatology (Arthritis Care and Research)*, 61(3):405–410, 2009.

[4] M. Cutolo, A. Sulli, C. Pizzorni, and S. Accardo. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. *The Journal of Rheumatology*, 27:155–60, 2000.

[5] M. Cutolo, W. Grassi, and M. Cerinic. Raynaud's phenomenon and the role of capillaroscopy. *Arthritis & Rheumatism*, 48(11):3023–3030, 2003.

[6] M. Cutolo, C. Pizzorni, and A. Sulli. Capillaroscopy. *Best Practice and Research Clinical Rheumatology*, 19(3):437–452, 2005.

[7] M. Cutolo, A. Sulli, M. E. Secchi, S. Paolino, and C. Pizzorni. Nailfold capillaroscopy is useful for the diagnosis and follow-up of autoimmune rheumatic diseases. a future tool for the analysis of micro-vascular heart involvement? *Rheumatology*, 45 Suppl 4 (ii):iv43–iv46, 2006.

[8] N.P. Doshi, G. Schaefer, and A. Merla. Enhancement of nailfold capillaroscopy images. In *IEEE-EMBS Int. Conference on Biomedical and Health Informatics*, 2012.

[9] N.P. Doshi, G. Schaefer, and A. Merla. Nailfold capillaroscopy pattern recognition using texture analysis. In *IEEE-EMBS Int. Conference on Biomedical and Health Informatics*, 2012.

[10] N.P. Doshi, G. Schaefer, and A. Merla. Robust nailfold capillary skeleton extraction. In *5th Int. Conference on Emerging Trends in Engineering and Technology*, pages 19–23, 2012.

[11] N.P. Doshi, G. Schaefer, and A. Merla. An evaluation of image enhancement techniques for capillary imaging. In *IEEE Int. Conference on Systems, Man, and Cybernetics*, 2012.

[12] W. Grassi, P. D. Medico, F. Izzo, and C. Cervini. Microvascular involvement in systemic sclerosis: Capillaroscopic findings. *Seminars in Arthritis and Rheumatism*, 30 (6):397–402, 2001.

[13] G. Hamar, G. Horvath, Z. Tarjan, and T. Virag. Markov chain based edge detection algorithm for evaluation of capillary microscopic images. In *11th Mediterranean Conference On Medical and Biomedical Engineering and Computing*, pages 818–821, 2007.

[14] M. Hasegawa. Dermoscopy findings of nailfold capillaries in connective tissue diseases. *The Journal of Dermatology*, 38:66–70, 2011.

[15] Q. Hu and F. Mahler. New system for image analysis in nailfold capillaroscopy. *Microcirculation*, 6(3):227–235, 1999.

[16] B. F. Jones, M. Oral, C. W. Morris, and E. F. J. Ring. A proposed taxonomy for nailfold capillaries based on their morphology. *IEEE Transactions on Medical Imaging*, 20(4): 333–341, 2001.

[17] H. S. Kim, M. K. Park, H. Y. Kim, and S. H. Park. Capillary dimension measured by computer-based digitalized image correlated with plasma endothelin-1 levels in pa-

tients with systemic sclerosis. *Clinical Rheumatology*, 29:247–254, 2010.

[18] F. Lefford and J. C. Edwards. Nailfold capillary microscopy in connective tissue disease: a quantitative morphological analysis. *Annals of the Rheumatic Diseases*, 45(9): 741–749, 1986.

[19] K. Lin, T. Cheng, and C. Chen. Clinical application of nailforld capillaroscopy in different rheumatic diseases. *Journal of Internal Medicine of Taiwan*, 20:238–247, 2009.

[20] L. Lo, J. Y. Chiang, and Y. S. Cai. Three-dimensional vision based nailfold morphological and hemodynamic analysis. In *IEEE 11th International Conference on Bioinformatics and Bioengineering*, pages 44 –51, 2011.

[21] H. R. Maricq and C. E. LeRoy. Patterns of finger capillary abnormalities in connective tissue disease by wide-field microscopy. *Arthritis & Rheumatism*, 16(5):619–628, 1973.

[22] E. Michoud, D. Poensin, and P. H. Carpentier. Digitized nailfold capillaroscopy. *VASA, Journal for vascular diseases*, 23(1):35–42, 1994.

[23] Z. Nagy and L. Czirjak. Nailfold digital capillaroscopy in 447 patients with connective tissue disease and raynaud's disease. *Journal of the European Academy of Dermatology and Venereology*, 18(1):62–68, 2004.

[24] M. Paradowski, U. Kaczmar, H. Kwasnicka, and K. Borysewicz. Capillary abnormalities detection using vessel thickness and curvature analysis. In *13th Int. Conference on Knowledge-Based and Intelligent Information and Engineering Systems*, pages 151–158, 2009.

[25] M. Paradowski, H. Kwasnicka, and K. Borysewicz. Avascular area detection in nailfold capillary images. In *International Multiconference on Computer Science and Information Technology*, pages 419–424, 2009.

[26] M. Paradowski, H. Kwasnicka, and K. Borysewicz. Capillary blood vessel tortuosity measurement using graph analysis. In *Knowledge-Based and Intelligent Information and Engineering Systems*, volume 5712, pages 135–142. 2009.

[27] M. Paradowski, H. Kwasnicka, and K. Borysewicz. Capillary blood vessel tracking using polar coordinates based model identification. In *Computer Recognition Systems 3*, volume 57, pages 499–506. 2009.

[28] G. Schaefer, B. Krawczyk, N.P. Doshi, and A. Merla. Scleroderma capillary pattern identification using texture descriptors and ensemble classification. In *35th IEEE EMBS Conference of the IEEE Engineering in Medicine and Biology*, 2013.

[29] A. Scheja, A. Akesson, I. Niewierowicz, L. Wallin, M. Wildt, and F. A. Wollheim. Computer based quantitative analysis of capillary abnormalities in systemic sclerosis and its relation to plasma concentration of von willebrand factor. *Annals of the Rheumatic Diseases*, 55(1):52–56, 1996.

[30] M. Tektonidou, E. Kaskani, F. N. Skopouli, and H. M. Moutsopoulos. Microvascular abnormalities in Sjogren's syndrome: nailfold capillaroscopy. *Rheumatology*, 38(9): 826–830, 1999.

[31] C. Wen, W. Liao, and K. Li. Classification framework for nailfold capillary microscopy images. In *10th IEEE Region Conference TENCON*, pages 1–4, 2007.

[32] C. Wen, T. Hsieh, W. Liao, J. Lan, D. Chen, K. Li, and Y. Tsai. A novel method for classification of high-resolution nailfold capillary microscopy images. In *1st IEEE International Conference on Ubi-Media Computing*, pages 513–518, 2008.