Mosaicking images of the corneal sub-basal nerve plexus using hierarchical block-based image registration

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Abstract

Introduction: Recent studies have shown in vivo confocal laser scanning microscopy (CLSM) of peripheral nerve fibres in the corneal sub-basal nerve plexus (SNP) to be a promising diagnostic tool for early detection of diabetic peripheral neuropathy. However, the small field of view in CLSM and the presence of ridge-like deformations of the SNP are the major limitations of this technique. We have previously published image processing algorithms for correcting motion artefacts in CLSM image sequences, reconstructing two-dimensional images of the SNP from CLSM volume scans, and generating SNP mosaics from reconstructed SNP images to address these limitations. Here we present a new approach to mosaicking the reconstructed SNP images.

Methods: The proposed mosaicking algorithm comprises three steps: rigid coarse registration, hierarchical block-based registration and mosaic formation. The coarse alignment of (partly overlapping) SNP images uses the phase-only correlation function. Because the SNP images are already devoid of most residual distortion artefacts the local registration error remaining after this step is relatively small. The hierarchical refinement of the registration result is performed by decomposing each image into a grid of uniform rectangular blocks and registering corresponding blocks of all images. Finally, the blocks at each grid position are analysed to exclude blocks that could not be registered precisely. The mosaic image is created by averaging the remaining blocks.

Results: The proposed algorithm has been tested on 8 previously recorded CLSM datasets consisting of 4 to 19 volume scans each. The resulting mosaic images show an improved signal-to-noise ratio compared to mosaics created with our previous implementation. In addition, erroneous duplications of nerve structures occasionally observed in previous results are almost completely avoided by the presented method.

Conclusion: The proposed algorithm to SNP image mosaicking is clearly superior to our previously published approach, providing a much more robust basis for morphological analysis of corneal nerve fibres.

1 Introduction

Diabetic peripheral neuropathy (DPN) is among the most common complications following and caused by diabetes mellitus. It is routinely diagnosed by the qualitative or quantitative assessment of nerve function such as reflex tests, vibration tests, heat and cold sensation or nerve conduction velocity. However, most of these tests can only diagnose pathological alterations in large peripheral nerves but are unable to detect small fibre neuropathies (although heat and cold sensation thresholds have been shown to possess some limited ability to do so). In addition, these tests are mostly subjective and, since they assess nerve function, they can usually only diagnose neuropathy when symptoms are already present.

As the small peripheral nerve fibres are often affected earlier than thicker fibres in the pathogenesis of DPN [1], the ability to detect small fibre neuropathy is important for the early diagnosis of DPN. The only reliable method to this end today is the histological assessment of peripheral nerve fibre morphology using skin biopsy, usually quantified in the measurement of the intra-epidermal nerve fibre density. The obvious drawback of this approach is its invasiveness, being painful or at least uncomfortable for the patient, bearing a potential risk of infections, and also prohibiting frequently repeated use for therapy monitoring.

Several recent studies have shown in vivo confocal laser scanning microscopy (CLSM) of peripheral nerve fibres in the sub-basal nerve plexus (SNP) of the cornea to be a promising diagnostic tool for early detection of DPN [2]. Due to the transparent nature of the cornea, this imaging technique allows non-invasive imaging and morphological assessment of corneal nerve structures. However, the high lateral resolution in CLSM is accompanied by a small field of view rendering single CLSM images insufficient for a reliable diagnosis. Therefore lateral images sequences are required to capture a larger area of the SNP. Moreover, the presence of ridge-like deformations in the otherwise flat arrangement of the SNP requires depth scans [3] (Image 1).

In order to address these two major limitations of CLSM we have previously published image processing algorithms for registration of CLSM image sequences including the correction of motion artefacts [4], reconstruction of two-
dimensional projection images of the SNP (simply referred to as SNP images hereafter) from registered CLSM volume scans by tracing the deformed SNP layer inside the volume data [3] (Image 1), and also an approach to creating extended mosaics of the SNP from SNP images [5]. The latter used the CLSM sequence registration scheme for the registration of the SNP images. Even though we achieved satisfying results for some data sets, we experienced significant misalignment problems with others, ultimately resulting in the dispersion or even duplication of image features after image fusion (Image 2).

The available image data was first processed by the aforementioned algorithms for motion artefact correction, volume reconstruction and SNP image reconstruction on the basis of single focus scans.

The subsequent step and the task at hand therefore is to first register and afterwards fuse the partly overlapping SNP images of a patient to receive a larger mosaic image. The inaccurate alignment we experienced with our previous approach [5] can be attributed primarily to inappropriate assumptions about the characteristics of the registration’s input images. For the original CLSM images each image row has been considered invariable, because of the very short time span required to capture a single image line. By design, the registration’s transformation space therefore allows image rows to be translated relative to each other but prohibits them being stretched or shrunk.

Essentially this means that distances between exactly horizontally separated image features can’t vary between images. This assumption is not valid for SNP images leading to the inaccurate alignment mentioned above and seen in Image 2.

The proposed block-based registration scheme is derived from the previous one but has been modified to allow for the missing degree of freedom of horizontal scaling. It also incorporates a hierarchical coarse-to-fine-approach for accurate and robust local distortion correction as well as a sharpening operation of the mosaic image at the end for enhanced image quality.

Image 3 shows the structure of the proposed mosaicking algorithm schematically. The distinct steps – rigid coarse registration, block-based registration, hierarchical iteration and mosaic formation – are described in detail in the following sections.

2 Methods

The CLSM images that were used for the development and testing of the new mosaicking algorithm had been acquired previously with a HRT (Heidelberg Retina Tomograph II equipped with a Rostock Cornea Module, Heidelberg Engineering GmbH, Heidelberg, Germany). The HRT system had been operated in its Oscillating Volume Scan mode, recording focus scan sequences of the SNP and the neighbouring tissue in the central region of the cornea. In this operation mode of the HRT the focal plane constantly oscillates back and forth between the basal epithelium and the anterior stroma layers of the cornea, passing through the SNP and Bowman’s membrane layers.

In chapter 2 we briefly analyse the underlying reasons behind the shortcomings of our previous approach to mosaicking SNP images and propose a new one, using a modified registration scheme. In chapter 3 we compare its results with the previous method. In chapter 4 we draw some final conclusions.
2.2 Block-based registration

After coarse registration of the SNP images the registration results are refined locally using a block-based registration scheme. This approach comprises three sub-steps: image decomposition into blocks, block-based registration involving a consistency check, and global refinement of block positions.

2.2.1 Image decomposition

By defining a regular grid over the global coordinate system the globally positioned SNP images are decomposed into uniform square blocks. As a result, under the assumption of relatively small residual local alignment errors after the coarse registration or a previous refinement level, all non-empty SNP image blocks at the same grid location show the same region of the SNP and can safely be assumed to possess considerable pairwise overlap.

2.2.2 Block-based registration

The block-based registration is done at each grid position independently. Similar to the rigid coarse registration step, an exhaustive pairwise registration procedure is performed over all (non-empty) blocks at a grid position by means of the phase-only correlation function. Registration results with correlation values below a small constant threshold value are discarded. In general the remaining registration results form an overdetermined system of linear equations (for a single grid position) that can be solved by the least squares method, yielding refined block positions. These results can now be used for an additional consistency check. If all registration results at the current grid position are consistent, the translation vector between the refined positions of each pair of corresponding blocks must approximately equal their respective registration result. Inconsistent block registrations reveal themselves by significant deviations. In this case the set of block registration results is reduced by removing the result showing the largest deviation and the block positions are recalculated with the reduced set of registrations. This step is repeated iteratively until a consistent state has been reached.

2.2.3 Global refinement of block positions

After block-based registration has terminated in a consistent state the global positioning is recalculated similarly to the coarse registration step, but at the block level instead of the level of entire images.

2.3 Hierarchical iteration

Several partly conflicting criteria must be considered in the decision on an appropriate block size for the block-based registration approach described above. On the one hand the primary aim is to choose the block size as small as possible in order to provide an optimal foundation for the detection and correction of local deformations in an SNP image. On the other hand a correct correlation can only be calculated if the residual local alignment error is less than half the block size. Additionally, smaller block sizes reduce the actual information content of the blocks and consequently the reliability of the correlation results. The hierarchical approach provides a solution, performing multiple iterations of the block-based registration with decreasing block size. In the present study two iterations with block sizes of 96×96 pixels and 32×32 pixels have been implemented.
2.4 Mosaic formation

After the final iteration of the block-based position refinement the mosaic image is created. The SNP images in general show a significant amount of pairwise overlap, in fact extended areas of the captured SNP region are quite often present in much more than just two SNP images. Under the assumption of good registration results this can be exploited in order to increase the signal-to-noise-ratio (SNR) of the mosaic images. Therefore the formation of the mosaic image is basically done by averaging the overlapping image information. Under this assumption only well-matching blocks contribute to this fusion. To this end we implemented another consistency check by correlating each single block with the average of all other blocks at the same grid location (once again using the phase-correlation function and rejecting blocks with insufficiently low correlation values). To prevent the irregular borders of the SNP images from being visible in the fused mosaic image pixel weights are implemented in the averaging process. All pixels in undefined regions of the SNP images or in rejected blocks are being assigned a weight of 0 while most other pixels are being assigned a weight of 1. The transition from weight 1 to weight 0 has been defined by a linear ramp over the width of 20 pixels in all border regions.

Finally, the mosaic image is being sharpened by the function $I' = I + (q - 1) \ast hpf(I)$ where $I$ is the mosaic image right after the weighted fusion, $hpf$ is a high pass filter function, $q$ is defined for each pixel as the square root of the number of SNP image blocks being averaged at that pixel and $I'$ is the sharpened mosaic image.

3 Results

The proposed algorithm has been tested on 8 previously recorded CLSM datasets consisting of 4 to 19 volume scans each and the results have been qualitatively compared to the results of our previous approach. The comparison clearly shows that the dispersion or duplication of image features occasionally observed in previous results is almost completely avoided by the proposed method (Image 4). In addition, subjective inspection suggests an improved image contrast in the new mosaic images while avoiding any visible increase in the noise level.

4 Conclusion

In summary this work describes a hierarchical block-based algorithm for the registration of SNP images. The results of a comparative study on 8 CLSM data sets of varying size demonstrate its superiority over our previously published approach. With the proposed mosaicking algorithm we can now set up a chain of image processing tools – most of them capable of working fully automated – for generating high quality mosaic images from CLSM volume scan sequences. These mosaic images can provide a robust basis for morphological analysis of corneal nerve fibres. The availability of automated robust image processing tools for CLSM image data will prove crucial to establishing this promising imaging technique for the early diagnosis and monitoring of DPN and other neuropathic disorders.

5 References