ABSTRACT
Diabetic retinopathy (DR) is a retinal vascular disease and is one of the most common causes of blindness worldwide. Proliferative diabetic retinopathy (PDR) is the most advanced stage of the disease and poses a high risk of severe visual impairment. PDR is characterised by the growth of abnormal new vessels known as neovascularisation. In this paper, we propose the use of the matched filter (MF) technique for vessel segmentation with emphasis on using two different sets of parameters to allow for the detection of new vessels. Parameters are selected to first increase and then decrease the MF response to new vessels, followed by thresholding to produce two separate binary vessel maps. The difference image removes most normal vessels and retains all possible new vessels, therefore making further analysis a much simpler task. Several steps are also included to reduce the detection of non-vessel objects (dark and bright lesions). Five local features associated with the morphology of the vasculature are used to create a feature set. Based on these features, regions of the retina are categorized as normal or abnormal using a k-nearest neighbour classifier. Sensitivity and specificity results were 100% and 70% respectively on a per image basis.

KEY WORDS
Diabetic retinopathy, new vessels, image processing, matched filter.

1 Introduction
Diabetic retinopathy (DR) is the damage to the retinal vasculature caused by high blood glucose levels, leading to progressive retinal damage that can end in loss to vision and blindness [1]. DR is recognized as the leading cause of blindness in the working-age population [2]. If DR is detected early enough, treatment can diminish visual loss [3],[4]. Often there are no symptoms in the early stages of DR, therefore screening is imperative for identification.

In the United Kingdom diabetic patients aged 12 and above are invited at least annually for retinal screening using digital photography to capture retinal images [5] (see figure 1). These images undergo thorough analysis by trained individuals, which can be very time consuming and costly due to the large diabetic population. Therefore this is a field that would greatly benefit from the introduction of automated detection systems [6].

The damage to the retinal blood vessels will cause blood and fluid to leak on the retina and forms features such as microaneurysms, haemorrhages, and exudates [7]. DR is a progressive disease, where areas of retinal ischaemia can develop and in an attempt of revascularization the growth of new blood vessels is triggered. New vessels represent the advanced stages of DR known as proliferative diabetic retinopathy (PDR), which pose a high risk of severe vision loss and therefore requires urgent referral to a specialist. This means automated systems not only need to be able to detect early stage DR, but also to detect and then prioritise PDR images to ensure immediate attention and treatment. The automatic detection of early stage DR has received a
lot of research attention, with studies investigating microaneurysm and small haemorrhage detection [8]-[10], and exudate detection [11]-[14]. In contrast, little work has been done to detect PDR.

New vessels appear as unregulated growth appearing off or near a vein often in the form of dense lacy networks which usually pass across the underlying veins and arteries. These tortuous and convoluted vessels are usually fine in calibre. Also new vessels can sometimes appear very faint and can be difficult to distinguish them from the background. Another difficult problem is that new vessels tend to grow away from the retinal surface towards the vitreous, and hence they can appear out of the focal plane of the photograph, resulting in a very blurry and obscure appearance. See figure 2 for examples of new vessels and other DR features.

![Figure 2.](image)

Figure 2. (a) Small haemorrhages, (b) exudates, (c) distinct new vessels, (d) obscure new vessels

One of the first steps of most new vessel detection methods will be the segmentation of all vessels, with the intention to further analyse this vessel map in the search for the presence of new vessels. There are a substantial number of methods reported in the literature for vessel segmentation, which can be generally categorised into the five main techniques based on matched filtering [15]-[17], mathematical morphology [18],[19], vessel tracking [20], unsupervised machine learning [21],[22] and supervised machine learning [23]-[26]. Despite the wealth of techniques most vessel segmentation techniques will struggle with new vessels due to their irregular appearance.

As mentioned earlier, only a handful of new vessel detection methods exist. The following methods all apply vessel segmentation prior to the analysis techniques mentioned here. Daxer [27], Karperien [28], described the retinal vasculature as a fractal. The fractal dimension is used to quantify the complexity of the pattern and therefore the presence of new vessel growth. Jelinek [29] extracted morphological features based on the derivatives of Gaussian wavelet derived data, these include curvature and entropy orientation. Goatman [30] developed a method to detect new vessels on the optic disc using a comprehensive set of 15 features including number of vessels, mean ridge strength and 3 tortuosity measures. Hassan [31] simply counted the number of vessels and the area of vessels locally as an indication of new vessels.

There are methods that don’t require vessel segmentation and therefore don’t have to deal with the issue of correctly segmenting all of the vascular structure, including difficult new vessels. Frame [32], Acharya [33], applied the grey level co-occurrence matrix to provide statistical texture measures to identify irregular distribution of pixel intensities associated with pathology. Agurto [34] utilized multi-scale amplitude modulation frequency modulation methods to perform spectral texture analysis for the characterization of retinal structures.

The main contribution of our research is the novel use of two different sets of parameters for the matched filter method to ensure two binary vessel maps are produced, a map containing all vascular structure and a map containing most of the normal vascular structure. Inspecting the difference image simplifies further analysis for the detection of new vessels. The organization of this paper is as follows. Section 2 describes details of the methodology. Section 3 presents the results. Finally, a discussion and conclusion is given in section 4.

## 2 Methodology

### 2.1 Pre-Processing

Retinal images often show lighting variations, poor contrast and noise, therefore pre-processing is required. The green colour plane was used in the analysis since it shows the best contrast between the vessels and the background retina. The median filter was applied to reduce noise. Non uniform illumination correction was performed using comprehensive colour normalisation. Local contrast enhancement was achieved by applying contrast limited adaptive histogram equalisation (CLAHE) [35]. High-boost filtering [36] was applied to sharpen the images.

### 2.2 Matched Filter

The Matched Filter (MF) was first proposed by [15] to detect vessels in retinal images. It makes use of the fact that the cross section of the vessels can be approximated by a Gaussian function. Thus, a Gaussian shaped filter can be used to “match” the vessels for detection. The MF is defined as

\[
g(x, y) = \exp(-x^2 / \sigma^2) - m, \quad \text{for } |x| \leq 3\sigma, \; |y| \leq L/2
\]

(1)

\(\sigma\) represents the scale of the filter. To ensure the inclusion of most of the Gaussian function the minimum span of
the x-axis should include the range $[3\sigma, 3\sigma]$. $m$ is the mean and it is used to normalize the mean value of the filter to zero so that the smooth background can be removed after filtering. $L$ is the length of the neighbourhood along the y-axis to smooth noise. In the implementation $g(x,y)$ is rotated to detect vessels of different orientations, see figure 3.

![Figure 3. Orientated matched filter](image)

The aim of the MF response is to detect all of the vasculature including new vessels. Thus, the parameters are selected to increase the MF response to new vessels. Three filters are applied at $\sigma = 1,3,5$ with the corresponding $L = 15,18,30$ pixels respectively to produce three MF response maps. The filters are applied in 8 different orientations. The different scales are selected to ensure vessels of varying widths are detected, including the fine calibre new vessels. $L$ is the length of the segment for which the vessel is assumed to have a fixed orientation. New vessels tend to be tortuous. Thus, the lengths of the filters are selected to be relatively short.

The MF response maps are each standardised against the perfect response of the filter used. This perfect response is achieved by placing on the retinal image a Gaussian function peaking at the maximum value of 255, with a scale and length corresponding to the filter used. A single threshold can be applied to all the MF response maps to produce binary vessel maps. A relatively low threshold is chosen to ensure that faint and obscure new vessel segments are retained. The three binary maps are fused with the logical OR operator.

The next stage produces a second binary vessel map from the MF with parameters selected to decrease sensitivity to new vessels. However, prior to this the current binary vessel map needs to be cleared up to remove detections of non-vessel objects, explained in the following section.

### 2.3 Bright and Dark Lesion Removal

A well known problem of the MF approach is that it responds not only to vessels but also to non-vessel edges. This problem also exists in other vessel detection methods. Exudates, also known as bright lesions, cause the most trouble. Their cross sections contain step edges at the edges of the bright lesions. The MF has strong responses to both the Gaussian functions (vessels) and the step edges. After thresholding, both the vessels and the edges of bright lesions will be detected. Bright lesion detection may cause large local densities and large curvatures which can be misclassified as new vessels.

A simple extension to the MF method using a pair of filters, the zero mean Gaussian filter (MF) and the first order derivative of the Gaussian filter, is used to distinguish the two types of structures. A full explanation of this scheme is provided by Zhang [17].

Microaneurysms and haemorrhages, known as dark lesions, are also non-vessel objects which can be wrongly detected. The parameters selected to increase the MF sensitivity towards new vessels, as well as the low threshold, may ensure all vasculature is segmented. However, they also cause an increased sensitivity to the detection of red lesions. A simple measure of circularity (see equation 2) and area from objects in the binary vessel map can be used to distinguish red lesions and other spurious objects in order to remove them.

\[
\text{Circularity} = 4\pi \cdot \frac{\text{area}}{\text{perimeter}^2} \quad (2)
\]

### 2.4 Straight Vessel Removal

A second binary vessel map is produced using the MF with parameters selected to decrease sensitivity to new vessels. Once again three filters are applied at the same scales as before. However, $L = 61$ pixels is selected for all filters. This longer length means that the MF is not sensitive to the tortuous new vessels and is instead only sensitive to relatively straight normal vessels. The filters are applied in 18 orientations instead of the 8 used before. With short filters a small misalignment in the angle with the vessel won’t throw the response off much. With long filters that small misalignment in the angle may result in the large majority of the filter not responding well to the long vessel. Therefore more orientations help to reduce the size of possible misalignments. Once more the MF response maps are standardised, thresholded and fused to produce a binary straight vessel map.

Two binary vessel maps are achieved. One map contains all vasculature including new vessels (from previous section) and the other map contains only straight normal vessels. The difference image results in a lot of the normal vasculature being removed and therefore all possible new vessels along with some normal vessels are left behind. This is a very simple and novel technique which significantly simplifies further analysis in the detection of new vessels. Consider a simple feature of vessel area within a local region to detect the dense networks of new vessels. There will be several regions of normal vasculature possessing a high vessel area, which may occur on/near the optic disc, at bifurcation points and at crossover points. Once straight vessel removal is performed it is now more likely that a region with high vessel area will be due only to new vessels. Therefore this simple feature has become more powerful in differentiating between normal and abnormal vessel regions. This technique will strengthen several other
features.

The removal of straight vessels may remove or damage segments from new vessel regions. Region growing is performed to return these regions to their original shape. A limited growth region growing method is applied to prevent the whole vascular map growing back. A circular disk of radius 5 pixels is centred over each pixel to limit its growth. This stage has the side-effect of bringing back a few additional normal vessel segments to the map.

See figure 4 which illustrates the methodology explained so far.

2.5 Features and Classification

The design of this method is for the classification of image regions containing new vessels. These new vessel regions can be categorised as containing many vessel segments, which appear in multiple orientations and also possess a tortuous nature. There is no intention to identify individual new vessel pixels or segments. That level of accuracy would be unattainable due to the often obscure appearance of new vessels. Even the creation of ground truths for training and testing at this level of accuracy would be an unrealistic task for any human observer. However, this level of accuracy is not essential from a clinical viewpoint.

The binary map needs to be converted into vessel segments prior to the measurements of features. The skeleton of the binary map is produced by means of morphological thinning, such that vessels are a single pixel in thickness. Vessel segments are created by removing bifurcation points which are pixels with more than two eight-way neighbours. Finally, small segments consisting of fewer than ten pixels are discarded.

A sub window of size 151 x 151 pixels was created in order to calculate local features associated with the morphology of the vascular structure. This window was scanned through the image and at each position the five features listed below were calculated.

1) Number of vessel pixels.
2) Number of vessel segments.
3) Number of vessel orientations.
4) Tortuosity.
5) Vessel density.

For the third feature, the end points of a segment are connected by a straight line. The acute angle the line makes with the x-axis is calculated. This is done for each segment within the sub window and the angle calculated is dropped into one of eight bins representing the range of angles. Therefore 8 orientations is the maximum amount. For the fourth feature, the tortuosity of each segment is calculated using the true length (using chain code) divided by Euclidean length. The mean tortuosity is calculated.
from all the segments within the sub window. For the fifth feature, a segment is dilated with a disk structuring element with a radius of 20 pixels. The number of vessel pixels within the dilated area is divided by the number pixels within the segment to give its vessel density. The mean vessel density is calculated from all segments within the sub window.

Features were normalised so that each feature has zero mean and unit standard deviation. The five features make up a feature vector used by a k-nearest neighbour (kNN) classifier to detect new vessel regions. If a sub window is classified as abnormal then only the central pixel is labelled as abnormal. After classification is complete all abnormal pixels are dilated by the size of the sub window to illustrate the new vessel regions.

3 Results

The proposed method was evaluated using the publicly available MESSIDOR database, kindly provided by the Messidor program partners [37]. These retinal images were captured using a colour video 3CCD camera on a Topcon TRC NW6 fundus camera with a 45 degree field of view. The images are at a resolution of 2240 x 1488 pixels. A selection of images was used to create a small data set containing 15 retinal images, 5 containing new vessels, 5 containing other forms of DR pathology and 5 healthy cases. In order to achieve quick preliminary results, standard ground truth images were not created. Instead 50 image patches of the size of the sub window were created from the data set and each patch was labelled as normal or abnormal by a human observer (ophthalmologist). These patches were used as training data for the classifier. Once trained, the classifier was tested on entire retinal images to detect local regions of new vessels. Prior to this, the human observer also marked with a cross the location of each new vessel region in the data set. This is required to assess the performance from testing. As there were too few images with new vessels for separate training and testing sets, the classifier was trained and tested simultaneously by leave-one-out cross validation. The classifier was trained using all the patches from all the images except those from the single test image, and this process was repeated for each image.

The five images containing new vessel overall consisted of a total of ten new vessel regions. Nine of these were successfully detected by the proposed algorithm. The algorithm also has the ability to delineate new vessel regions, however the following results are given on a per image basis as this is more useful for clinical application. A sensitivity of 100% and a specificity of 70% were achieved. Examples of the successfully classified images are given in figure 5, with the window boxes indicating new vessel regions. Figure 5 also includes an example of an image correctly classified as containing no new vessel regions and an image wrongly classified as containing new vessel regions. Table 1 shows these results along with the reported results from other new vessel detection methods.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jelinek[29]</td>
<td>94%</td>
<td>82%</td>
<td>per image</td>
</tr>
<tr>
<td>Goatman [30]</td>
<td>84.2%</td>
<td>85.9%</td>
<td>per image</td>
</tr>
<tr>
<td>Hassan [31]</td>
<td>63.9%</td>
<td>89.4%</td>
<td>per pixel</td>
</tr>
<tr>
<td>Proposed</td>
<td>100%</td>
<td>70%</td>
<td>per image</td>
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</table>

4 Discussion and Conclusion

In this paper, we have presented an effective method to detect the presence of new vessels based on the MF technique with two sets of parameters and a five dimensional feature vector used to analyse the local retinal vasculature.

The main contribution of this paper is the use of the MF with two different sets of parameters to produce two binary vessel maps. The first binary map puts emphasis on how to ensure new vessels are included in the segmentation, which is a topic not discussed sufficiently by other methodologies. The removal of the second binary map is a simple and novel technique that helps to simplify further analysis. Another important point emphasised in this work, is that high vessel area is not sufficient alone to categorise new vessel regions. The feature vector used underlines that analysis of the morphology of the vasculature is very important. This method has also been shown to successfully handle other DR pathology to reduce false detections. Figure 5(c) shows false detections are avoided despite the presence of large amounts of bright lesions.

The results show a maximum sensitivity which is at the cost of a lower specificity. Whilst this maximum sensitivity is unlikely to remain if tested on a large data set, it is still likely to be very high. These results are promising when considering the requirements for clinical application. In U.K. screening programmes it is the task of trained individuals to assess and label images according to their severity to determine the urgency of referral to an eye specialist. It is considered a serious breach in protocol if an image with proliferative DR is either missed or delayed in referral. Therefore these trained individuals are often advised to award the higher severity label whenever they are unsure of the presence of proliferative DR.

The false detections that have been produced appear to be caused by areas of dilated capillaries. From figure 5(d) the false detection shown appears at first glance to be caused by the presence of red lesions. Upon closer analysis, it was shown that these red lesions were all successfully removed and therefore were not the cause. Instead in regions of false detections there appears to be the presence of faint vessels. These are clearly not new vessels however they may be dilated capillaries also known as intra-retinal microvascular abnormalities (IRMA). These represent a stage of DR that indicates an increased risk of the progression.
of new vessels. These can be very difficult to differentiate from new vessels. Another cause for false detections is due to bright lesions. This method has been shown to handle bright lesions using a scheme proposed by Zhang [17]. Bright lesions have the characteristic of possessing a cross section that contains step edges, these can be used to differentiate them from vessels. The problem occurs only if bright lesions are in close proximity. Now their cross section losses their characteristic of appearing as step edges and instead the space in between bright lesions resembles that of a vessel. These are the main issues to tackle in the development of this algorithm.

An initial step in further development would be to produce a ROC curve in order to establish if an operating point exists that can considerably reduce the false positives whilst retaining a high sensitivity. This can be produced by applying a kNN classifier to assign probabilities of belonging to each class. A threshold is selected to determine the probability that defines a new vessel region, therefore varying this threshold allows for a ROC curve to be produced.

The reported results of other methodologies have been included in table 1. However, comparisons are difficult to make as no standard data sets have been used for testing. New vessel regions are known to vary largely in terms of how distinctive they appear. Therefore data sets can be created only using distinct new vessel regions in order to enhance performance measures of the algorithm. The data set used for this paper includes images with a varied range of new vessel regions. Also there is only a handful of methods in this field that have published results and these tend to vary in terms of their application. Jelinek [29] applied their method on fluorescein images which possess a very high contrast. However, this study is not appropriate for DR screening programmes as they do not capture images of this type. Goatman [30] developed a method that detects new vessels only on the optic disc.

Now that promising preliminary results have been achieved, further development of this method will include the creation on ground truth images for training and testing. These will be created by a human observer labelling...
new vessel regions with a marker of the same size as the sub window. The marker will be spread across new vessel regions, however only the centre pixels will be labelled. This will result in entire images being used for training and not just selected patches. This will also allow better performance analysis from the testing in terms of how well the new vessel regions are delineated. Despite the main target of this method being just the identification of the presence of new vessels, their accurate delineation can be useful for further pathological assessment.

Other intended further developments involve applying the two sets of parameters framework to more advanced vessel segmentation methods, such as the use of Gabor wavelets with supervised machine learning. A more interesting development is to replace the manual selection of the two sets of parameters which has to be performed by an experienced individual. This can be achieved by using an optimization technique for the automated selection of parameters. This essentially explores the whole parameter space looking for the best combination of parameters for each set which results in the difference image containing an optimal amount of new vessels and normal vessels decided by a cost function. However, to achieve such a cost function would require the creation of ground truths labelling new vessel pixels which can be a very difficult task to perform. The introduction of such a technique has the potential to remove all pre-determined parameters and therefore provides a more general approach. This means the algorithm can be applied regardless of image resolution and it requires no user input. Most importantly the algorithm would be capable of producing a selection of parameters superior to a manual selection.

All current methods are designed at the detection of new vessel regions, which can be defined as a dense lacy network of unregulated vessel growth. However, there can be some deviation away from this description, in which new vessels may occasionally appear as single vessels or small loops. These cause very subtle changes to the vasculature, therefore all current methods (including this method) are likely to fail in the detection of such cases. Their detection is an extremely difficult task and would require a novel and radical approach. Another variation to new vessels is that their presence can cause other retinal features to appear. For example the rapture of new vessels is that their presence can cause other retinal network formations, as well as single new vessels and also the associated features mentioned above. This data set would help the image processing community to appreciate the full scale of the problem to tackle.

We can conclude that this paper has successfully demonstrated the automated detection of new vessels. Although it remains a very challenging task to be capable of detecting all variations of proliferative DR and is therefore a field that requires continued research efforts. This paper should help promote these efforts by bringing awareness to the image processing community of the importance of the detection of proliferative DR.

References


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