A Novel Method for Micro Aneurysm Detection and Diabetic Retinopathy Diagnosis

Adarsh.P
PG Scholar, Dept. of ECE
RVS College of Engg & Tech
Coimbatore, Tamilnadu, India

D.Jeyakumari
Assoc. Professor, Dept. of ECE
RVS College of Engg & Tech
Coimbatore, Tamilnadu, India

ABSTRACT
In medical image processing a reliable means of microaneurysms detection in digital retinal images is still an open issue. In this paper, we propose a computerized scheme to improve microaneurysm detection. Image preprocessing is followed by the detection of microaneurysm regions using edge detection. Regions corresponding to blood vessels and bright lesions were removed by image segmentation from the fundus images. Unlike other well-known approaches of machine learning classifiers, we propose a combination of microaneurysm detection and diabetic retinopathy grading using SVM. Microaneurysm detection is decisive in diabetic retinopathy (DR) grading, so we evaluated our approach on four publicly available databases, where a promising AUC $\geq$ 0.96 is obtained in a "normal" or "abnormal"-type classification based on the detected microaneurysms. The performance assessment of the automated system is based on Sensitivity, Specificity, and Accuracy together with the ROC curves.

General Terms
Medical imaging, classification

Keywords
Diabetic Retinopathy, Microaneurysms detection, SVM, ROC

1. INTRODUCTION
Diabetic retinopathy (DR) is a serious eye disease that occurs due to diabetes mellitus and it has grown as the most common cause of blindness in the present world. Based on latest reports by 2030 there is an epidemic rise of 4.4% in the global prevalence of diabetes [1]. Diabetic retinopathy is an asymptomatic disorder hence an effective treatment must be provided to prevent vision loss. The risk of blindness can be reduced by 50% with an early treatment to prevent the development of diabetic retinopathy [2]-[4]. Hence, the solution is to adopt a mass screening process of patients suffering from diabetes, as manual grading is resource demanding and slow. Therefore, much effort has to be made to develop a reliable computer aided diagnosis (CAD) systems purely based on color fundus images.

With a large number of patients, the workload of local ophthalmologists is highly unsubstantial. So the automated detection systems should be able to limit the severity of the disease and pave assistance to the ophthalmologists in diagnosing and remedying the disease, effectively. To build such automated systems, different modules are needed for analyzing retinal anatomical features such as fovea, optic disc, blood vessels, and common diabetic pathologies, such as hemorrhages, microaneurysms, and exudates.

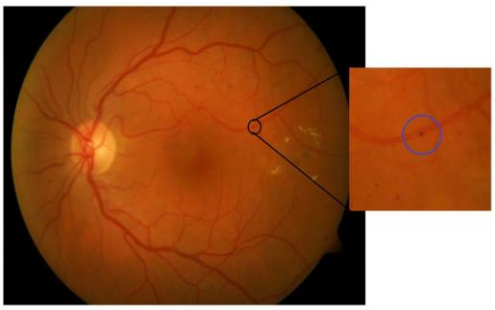

Fig 1: Sample digital fundus image with a MA.

Fundus images are obtained non-invasively, through pupil dilation, using a digital camera and a flash. Typically, the resolution of state-of-the-art system is very good, images being digitized. Microaneurysms (MAs) are the earliest clinical symptoms of DR which is referred as non-proliferative stage. These are tiny swellings in the blood vessel walls which appear as small red dots on the retina. They continue to get worse with the progress of the disease. If the early signs are not treated immediately, the disease will quickly transform to proliferative stage where new fragile vessels will born (neovascularization), threatening eye sight and may cause retinal detachment. With this motivation we have concentrated on detecting microaneurysms as the prime marker of DR disease as they are directly related to retinal hemorrhage and vision loss, and are the single most important retinal lesion difficult to detect in fundus images.

2. BACKGROUND
Cree et al. [5] reported a method which addresses of suppressing vessel like structures using a top hat step and then output is thresholded and region growing is carried out to leave a set of candidate points. Usher et al. adopted the use of adaptive intensity thresholding together with an edge enhancement operation for an efficient detection of MAs [7]. Fleming et al. method consisted of contrast normalization and top hat morphological operations together with KNN classifier [6]. Grisan et al. made an attempt to detect the dark lesions based on local thresholding and pixel density [8]. Xu et al. proposed that red dots can be detected using mathematical morphological black top hat and their features estimated by SVM classifier [9]. A novel approach using multi-scale Gaussian correlation filtering and sparse representation classifier was defined in [10]. Then a two stage approach was suggested based on Radon transformation without the need of explicit training [11]. Niemeijer et al. investigated the detection of red regions by pixel classification and feature analysis [14]. A method based on double ring

filter in non-contrast images of the retinal fundus was mentioned in [13]. In [12] an ensemble-based framework was realized to improve microaneurysm detection using preprocessing methods and candidate extractors.

Since all the above mentioned algorithms were rather complex, and time consuming, the overall efficiency of the system was affected. Here, our aim is to incorporate the effectiveness of computer aided diagnosis towards automatic detection of red lesions. The paper focuses on extracting features in a fundus image using different morphological operations. After feature selection, SVM supervised classifier is applied to remove the potentially false detections based on some assumptions and classifies the images into normal and abnormal based on the presence and absence of MAs.

This work is organized as follows. Section 3 describes the microaneurysm detection, feature extraction, feature selection and supervised classifier. Section 4 presents the experimental results and ROC analysis for performance evaluation, which are summarized and discussed in Section 5.

3. PROPOSED METHOD

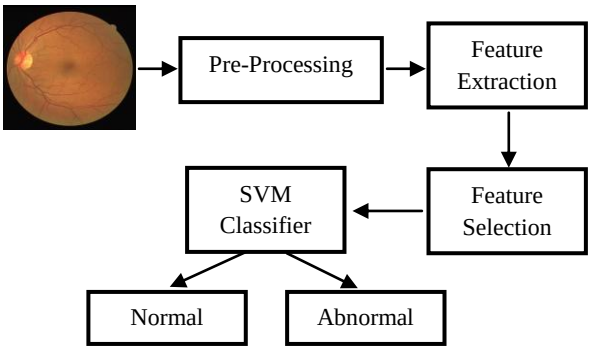

Fig 2: Block diagram of overall diagnosis system for DR

3.1 Materials

Lot of sources is available for obtaining high resolution fundus images viz color fundus cameras, or by angiograms obtained with fluorescein as a tracer. In this work we have taken a large dataset which consist of 420 images which are used for both training and testing of the method. Entire database of images were made with the help of four publicly available databases which have noticeable changes in contrast, illumination, color, quality etc. All these databases have ground truths where all the images are classified by an ophthalmologist based on the type of lesions (exudates/ microaneurysms). An image without red lesions is considered normal and the one with red lesions is considered abnormal. Details of the various sources of the images are summarized in Table 1.

Table 1. Dataset divided into normal and abnormal classes

Source	Total	Normal	Abnormal
DIARETDB0	130	20	110
DMED	169	69	100
STARE	81	30	51
DRIVE	40	33	7
Total	420	152	268

3.2 Pre-Processing

Most of the medical image processes starts with the pre-processing stage, which has to be applied before feature extraction. The image resolution of the datasets varied from 768 x 576 to 2196 x 1958 pixels. Initially rescaling is done on the input images into a standard size of 720 ×576 pixels while preserving the original aspect ratio. Then the green channel image is selected from the rescaled image for our operations. This is due to very low contrast in the blue channel and high saturation in the red channel for the retinal images. Later on contrast enhancement is applied using adaptive histogram equalization to the gray scale image. Contrast limited adaptive histogram equalization (CLAHE) is a common technique and it highlights the lesion visibility very effectively. The image is partitioned into disjoint areas, and in each area local histogram equalization is employed. Then to eliminate the boundaries between regions, bilinear interpolation is applied.

3.3 Microaneurysm Detection

The most challenging part in DR diagnosis is to detect microaneurysms, which are the earliest clinical signs of DR. MAs are actually the focal dilatations happening in the retinal capillaries. They are localized saccular distensions of the weakened capillary walls and appear as small round dark red dots (~15 to 60 microns in diameter) on the retinal surface. In the later stages they result is serious vision problems, hence the detection of MAs must be within the early stage. The grayscale image is used to create circular border and mask for optical disk. Initially the green channel image is used to find edges using canny method; before removing the circular border to fill the enclosed small area. Then circular border, edges and larger areas are removed. Exudates being the bright spots on the image, to make them visible adaptive histogram equalization is applied twice followed by image segmentation. Resulting bright feature areas are undergone comparison using AND logic with large area removed image in order to remove exudates. Following this the blood vessels and optical disk are removed to give the microaneurysm alone.

3.3.1 Border Formation

Due to better efficiency grayscale image is used instead of the green channel image for border detection. The method uses canny method to detect the edges. Then the circular region is enclosed with a top and bottom bar. Using the function "imfill" the region is filled. When the dilated image is subtracted with the eroded image the circular border is obtained.

3.3.2 Mask Creation

The mask creation for optical disk is also carried using grayscale image because of its upper hand in the detection process. A serious concern with the optical disk is that, as it is made up of a group of bright spots; using loops to locate the largest value will be ineffective. Initially the max value for each of the 720 columns of the image has to be determined before finding the largest value. Then coordinates (row and column) of all brightest point(s) are found and median is taken in case of multiple points. Applying these coordinates the circular mask is drawn.

3.3.3 Algorithm

Input: Color fundus image.

Output: Image containing only the microaneurysm.

Step 1: The RGB image is first pre-processed to standardize its size to 576 x 720 and intensity of the grayscale image is then adjusted.

Step 2: The image's contrast is stretched by applying adaptive histogram equalization before using edge detection (canny method) to detect the outlines of the image.

Step 3: The circular border is then removed before applying the function "imfill" to fill up the enclosed area.

Step 4: The holes (microaneurysms and noise) image is obtained by subtracting away the edges image and removing the larger area using function "bwareaopen".

Step 5: As the exudates are bright spots on the image, the image is applied with adaptive histogram equalization twice and image segmentation to "bring" out the exudates.

Step 6: These bright features are compared with Step 4 outcome using AND logic to remove the exudates.

Step 7: Blood vessels are extracted by applying adaptive histogram equalization twice and image segmentation of another threshold value. A clearer image of blood vessels is acquired after removing the small area of noise.

Step 8: This image is compared using AND logic with the result from the Step 6 to remove the vessels.

Step 9: The final microaneurysms image is obtained after removing the small noise and optical disk area.

3.4 Feature Extraction

Following the pre-processing stage features of the fundus images namely area of microaneurysms and texture properties are extracted. These analytics are later used by the classifier to categorize the images accurately.

3.4.1 Area of Microaneurysms

This is obtained by using two loops to count the number of pixels with binary 1 (white) in the final segmented microaneurysms image.

3.4.2 Texture Features

Texture analysis of an image is the study of mutual relationship among intensity values of neighboring pixels repeated over an area larger than the size of the relationship. The texture features considered for this work are mean, standard deviation (SD), third moment, entropy and homogeneity. Co-occurrence matrix defines the spatial distribution of gray level from which homogeneity feature can be acquired.

$$\text{Mean, } \mu = \sum_{i=0}^{N-1}\sum_{j=0}^{N-1} iP_{i,j} \quad (1)$$

$$\text{SD, } \sigma = \sqrt{\sum_{i=0}^{N-1}\sum_{j=0}^{N-1} P_{i,j}(i-\mu)^2} \quad (2)$$

$$\text{Third moment, } \mu_i = \sum_{i=0}^{L-1} (z_i - m)^3 p(z_i) \quad (3)$$

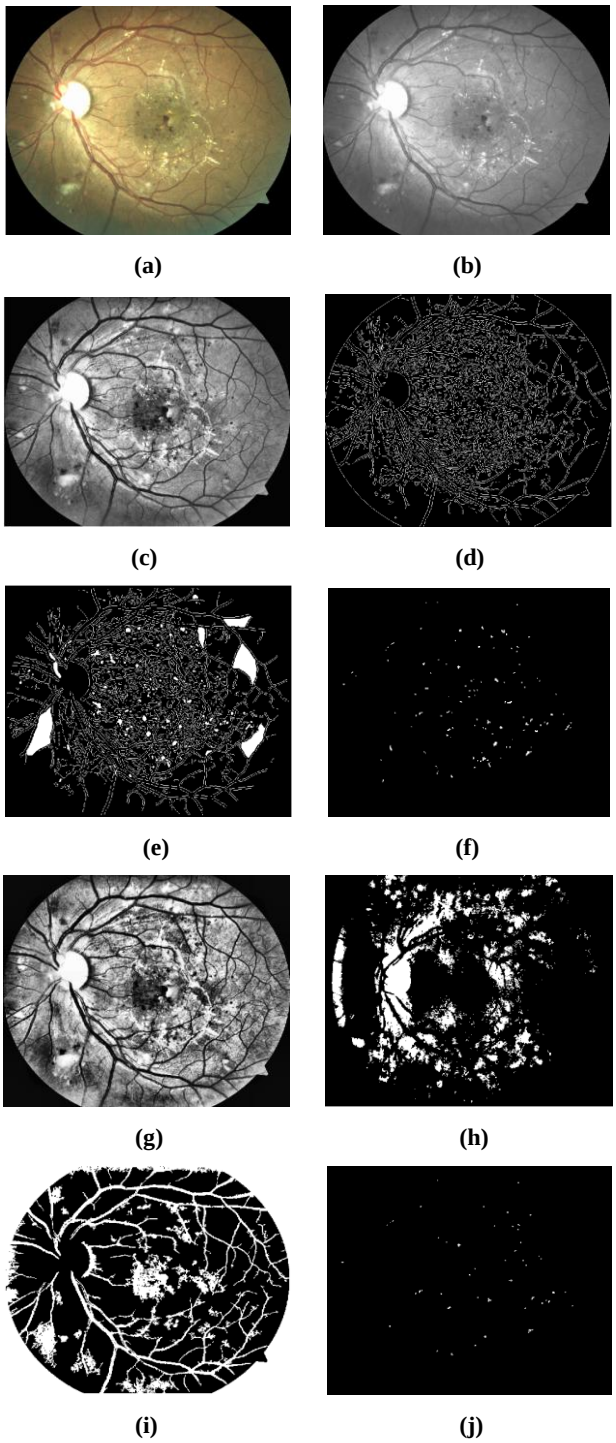

Fig 3: Illustration of the steps in microaneurysm detection with image from DMED database (a) Input (b) Intensity adjusted grayscale image (c) Histogram equalized (d) Edge detection (e) Initial MAs detected (f) Removing the larger area (g) Histogram equalization done twice (h) After segmentation (i) Blood vessels after removing small area of noise (j) Final MAs.

$$\text{Entropy} = -\sum p \log_2 p \quad (4)$$

$$\text{Homogeneity} = \sum_{i,j} \frac{p(i,j)}{1+|i-j|} \quad (5)$$

3.5 Feature Selection

There are now total of 6 features which include one area calculation (microaneurysms) and five texture features. To select the significant features among these we have used a significance test. Significance test is to calculate statistically whether groups of data are happened by chance or true occurrence or the level of true occurrence. This significance level is denoted by the term probability value (p-value). When the p-value is low, it indicates the set of data is statistically significant. For significance test analysis in this work we are using Anova (Analysis of variance) test. Anova test is based on null hypothesis that makes the test statistic to follow a distribution if a null hypothesis is true. All the features are checked with Anova to acquire clinically significant ones. Thus, when p-value < 0.05 it will result more difference between the abnormal and normal sets of feature data. In this way area of microaneurysms, mean, third moment and entropy are found as statistically significant sets of features and are used in the SVM classifier.

3.6 Support Vector Machine (SVM)

The supervised classifier used for the work is support vector machine (SVM). The original SVM algorithm was developed by Vladimir N. Vapnik and the current standard incarnation (soft margin) was suggested by Vapnik and Corinna Cortes in 1995.The basic SVM requires a set of feedback information and forecasts, for each given feedback, which of two possible sessions forms the outcome, making it a non-probabilistic binary linear classifier. SVM is fully dependent on strong concepts from the wide area of statistical learning theory as per structural risk minimization. In higher dimensional spaces the performance offered by binary SVM is further better. The primary function of binary SVM is to find a hyper-plane that best distinguishes the vectors from 2 classes in feature space simultaneously maximizing the margin between each class to the hyperplane. It includes both linear and nonlinear methods for this hyperplane creation [15]. If the two classes are linearly separable, SVM computes the optimal separating hyper-plane with the maximum margin by minimizing the objective function $\|w\|^2$ subject to:

$$(x_i \cdot w + b)y_i \geq 1, \tag{7}$$

The main limitation of SVM linear classifier occurs when a non-linear classification is needed. To resolve these nonlinear boundary problems, Kernel functions can be used. Since entire procedure works over manual training of data, the data must be of good quality and statistically significant. The training process analyzes training data to find an optimal way to classify images into their respective classes. As the overall performance relies on the manual labor, it is referred as a supervised classifier. In accordance with the selected features the classification parameters are produced using SVM learning algorithm, which are used to classify the images into normal or abnormal categories.

4. EXPERIMENTAL RESULTS

To investigate the efficiency of the suggested technique, the algorithm was run on entire datasets and the results for microaneurysm detection were gathered.

4.1 Performance Evaluation

Normal run time of Matlab code per image was estimated to be 15 seconds using a PC with an Intel i3 Processor and 2 GB RAM. All the data bases are individually used for training and testing the classifier. The samples of each dataset are divided into 90% training and 10% for testing categories. Then the SVM classifier is trained with the training data set. Later the binary SVM classifier is tested with each of the test data set of the corresponding database. To evaluate the performance of the approach; performance metrics such as sensitivity, specificity and accuracy are calculated using the equations given below:

$$\text{Sensitivity}(\%) = \frac{TP}{TP+FN} \times 100\% \tag{8}$$

$$\text{Specificity}(\%) = \frac{TN}{TN+FP} \times 100\% \tag{9}$$

$$\text{Accuracy}(\%) = \frac{TP+TN}{N} \times 100\% \tag{10}$$

The terms used in the equations above are true positive (TP), true negative (TN), false positive (FP), false negative (FN) and total number of images (N). Results obtained for each test set of individual databases are given in Table 2.

Table 2. Performance Metrics of the Datasets

Source	Sensitivity (%)	Specificity (%)	Accuracy (%)
DIARETDB0	90	94.3	96
DMED	91.2	93	94.6
STARE	88.9	91.2	93
DRIVE	86.4	91.7	93.5
Average	89.125	92.55	95.025

4.2 Receiver Operating Characteristics

Receiver operating characteristics (ROC) curves are plotted of true positive rate (TPR) versus false positive rate (FPR) for varying thresholds on the posterior probabilities. TPR is also known as sensitivity and FPR is also known as 1- specificity. A pair formed by TPR and FPR value is plotted as a graph for each threshold value resulting in a curve as shown in Figs. 4. The performance of the method will be better when a ROC curve approaches closer to the top left corner [16].

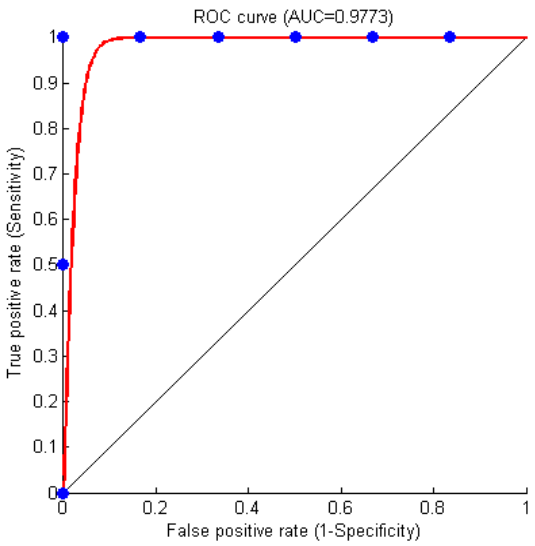

Fig 4: ROC curve for microaneurysm classification on the DIARETDB0 database using the SVM classifier.

When an area under ROC curve A_z= 1 it reflects that system completely agrees with the ground truth segmentations. Area under the ROC curve (AUC) gives the classifier's performance across the whole range of cut-off points. From Table 2 it is clear that our method performs well for all the databases. Here the AUC value is above 0.96 which reveals that the performance of classifier is excellent.

5. DISCUSSION AND CONCLUSION

In this work, we have investigated techniques with the objective of identifying and categorizing DR pathologies with the help of an intelligent computer aided diagnostic system. The results of all the performance metrics, shows recommended strategy really outperforms the earlier invented DR analysis methods. A brief comparison of the proposed method with earlier methods as described in their literary works is given in Table 3. From this comparison it is obvious that the recommended method is really competitive. One of the drawbacks with SVM is the laborious task involved in the manual training of information. But when working with autopsy, performance is more important than time which is assured in our method. Sturdiness and accuracy of the technique was calculated against ophthalmologists' hand drawn ground-truth. All the outcomes acquired are really encouraging. The performance of the method can be further improved by incorporating other learning techniques.

. **Table 3. Comparison of Results with Previous Methods**

Author	Number of Images	Sensitivity (%)	Specificity (%)
Sinthaniyothin	30	88.5	99.7
Wang et al.	154	100	70
Chutatape	35	100	71
Proposed Method	420	89.125	95.025

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