Automatic Screening of Retinal Lesions for Grading Diabetic Retinopathy

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Abstract: *Diabetic Retinopathy (DR) is a diabetical retinal syndrom. Large number of patients have been suffered from blindness due to DR as compared to other diseases. Priliminary detection of DR is a critical quest of medical image processing. Retinal Biomarkers are termed as Microaneurysms (MAs), Haemorrhages (HMAs) and Exudates (EXs) that are helpful to grade Non-Proliferative DR (NPDR) at different stages. This research work contributes an automatic design for the retinal lesions screening to grade DR system. The system is comprised of unique preprocessing determination of biomarkers and formulation of profile set for classification. During preprocessing, Contrast Limited Adaptive Histogram Equalization (CLAHE) is utilized and Independent Component Analysis (ICA) is extended with Curve Fitting Technique (CFT) to eliminate blood vessels and optic disc as well as to detect biomarkers from the digital retinal image. Subsequent, NPDR lesions based distinct eleven features are deduced for the purpose of classification. Experiments are performed using a fundus image database. The proposed method is appropriate for initial grading of DR.*

Keywords: *DR, CLAHE, ICA, CFT, biomarkers.*

Received December 10, 2015; accepted March 24, 2016

1. Introduction

Diabetes is a quickly expanding disease on the planet [49]. In Pakistan alone; over 6.2 million people having Diabetic Retinopathy (DR) type disease are already at the risk of becoming blind [16]. Diabetes is not diagnosed in large number of people, which may leads to blindness. Diabetes damages sensitive tissues retinal blood vessels causing blindness [51]. Many problems can follow diabetes, one of which is DR, resulting complete blindness. A diabetic Mellitus triggers DR, which is an eye vulnerable sickness. It affects the retina of the eye. It is categorized into four phases with respect to severity level; mild non-proliferative DR, moderate Non-Proliferative DR (NPDR), severe NPDR and proliferative DR. Long-term diabetes is said to be a primary cause of DR which causes permanent vision loss. This disease occurs in steps. Patient does not feel any sign of visual weakening at the early phase. The wounds existing on the retina determines the concentration of DR.

A human retina is comprised of several parts for example blood vessels, macula, fovea and the optic disc. There are two phases of classification for the DR; NPDR and Proliferative DR (PDR). On the injury of the blood vessels in retina, a fluid starts to be discharged. Consequently, retina turns into wet and swollen. At this phase, several identifications of retinopathy persist. For illustration, Hemorrhages (HMAs), Microaneury`Sms (MAs), Exudates hard as well as soft (EXs) and Inter-Retinal Microvascular Abnormalities (IRMA). The growth of new erratic blood vessels in retina produces PDR. PDR may cause complete blindness [31] as it is the last phase of DR. The problem in DR yields Diabetic Macular Edema (DME) which is the basis for the blindness [48]. A diabetic is a communal sickness. Here, pancreas fails to produce adequate insulin. As an outcome of which unmanagable glucose level arises in the body. This constant glucose level results problem in the eye termed as diabetic retinopathy [12]. This illness happens because of microangiopathy which disturbs different regions of the eye:

1. Capillaries.
2. Venues.
3. Arterioles. There are two primary reasons for this retinal injury:
    1. Microvascular blockage.
    2. Microvascular leakage.

With the increase of blood glucose level, changes in the retinal blood vessels are sparked, resulting retinopathy [29, 44]. Accompanied by microvascular blockage and leakage, occassionally development of anomalous fresh blood vessels on the retinal surface is a reason for the retinopathy. The existence of MAs in the eye is initial indication of retinopathy. Previously, victim does not sense any DR. This may advanced to permanent damage of sightedness. Atypically, both eyes are influenced by DR [28]. Also, alteration hapens in the mass of blood vessels (swelling) Microaneurysm, Exudates, Hemorrhage along with new blood vessels develop. Earlier detection of such changes helps in the selection of further treatement steps [43]. Exudates are the primary signs of DR and

the primary cause of blindness. Early screening process can help restrain its development. In this paper, the symptoms mentioned above of DR will be considered, and an automated system for screening of DR at early stages will be presented.

Mostly, the principal reason of DR is visual disability. Fundus images DR images helps to diagnose the disease. DR can be significantly be identified by the use of digital images. Different color spaces can be determined is the segmented region. An economical Computer Aided Diagnosis System (CAD) is used in this research work. Blood vessels, optic discs and Exudates in the digital fundus images are extracted. Exudates are identified as the combination of protein and lipid in the retina. They color is white or cream. Bright lesions and reflection is observed on Exudates. They signify associated hazards of retinal edema or swelling. Elimination of retinal constituents identified as vessel tree and optic disc is primary important step. Exudates residents are emphasized after detachment of other structures.

With the growth in the sum of DR patients', CAD obtained significant recognition because of slow work of traditional analysis of fundus images. Literature regarding CAD system for DR grading pertains differences, we will consider DR grading methods based on biomarker as discussed earlier. By using the CAD system, noteworthy analysis has been performed to identify the DR from fundus images. Researchers selected various biomarkers to determine vascular diseases. These vascular based identification systems are discussed in [4]. A biomarker related to vascular is employed. A grading system is thrived out of it.. Likewise, other biomarkers comprise retinal MAs [10, 37], EXs [11, 25], HMAs [18, 37], distances between the EXs and fovea to plan a ranking system for the disease. Using the stated image based biomarkers, numerous ranking or grading systems incorporates mutual assessment of versatile features. After feature extraction, researches determine the level of DR with the help of a classifier such as Raja and Vasuki [34] analyzed the EXs at fovea region to classify the normal and abnormal DR images while classification is achieved by Support Vector Machine (SVM). in the same way, classifier based DR grading system is presented by Tariq *et al*. [45] in which authors extract fifteen different features based on Exs, MAs, and HMAs. Microaneurysm based automatic DR screening system is introduced in [5]. Murray *et al*. [27] introduce Real-time screening system build on Amplitude Modulation Frequency Modulation (AM-FM) automated grading system. In this system, authors extract the retinal features and classify fundus images into two classes' namely normal or abnormal grade using supervised learning. Klein *et al*. [21] also introduced a system in to monitor DR progression by analyzing changes in the diameter of retinal vessels. Similar, retinal vessel segmentation discussed in [6]. Contextual information is vital in medical images. Contextual data is employed for the discovery and distinguishability of bright lesion in the retinal image. Contextual data is also used to identify coronary classification and hard exudates in the CT scan images [9, 38]. Hashim and Hashim [13] performed on contextual information at image level for automatic screening on DR. Although the advantages of the CAD mentioned above system are used systematic analyzes with the same purpose, still need more improvement to diagnose DR at an early stage.

This paper investigates automatic grading system for the recogonition and classification of DR at different levels. In the proposed system, Curve Fitting Technique (CFT) based on thresholding is introduced for lesion extraction. Moreover, eleven potential features based on NPDR lesions are extracted and ensemble for classification purpose. More detail of proposed system is discussed in the upcoming sections.

2. System Overview

There are two phases of DR; detection and classification. Fundus digital images are used by the DR to identify all disease signs. Biomarkers are then extracted. This research emphasized on the stage wise detection of EXs and Mas for grading of DR. The new system has the stages named candidate region preprocessing with feature extraction and DR grading. Figure 1 identifies the flow of our proposed work.

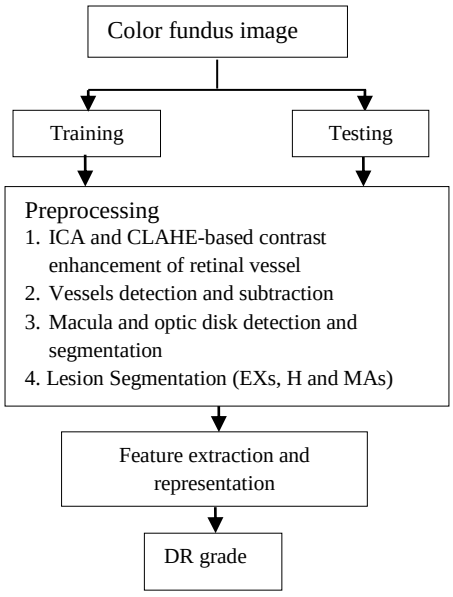


Figure 1. Flow diagram of our system.

2.1. Candidate Region Preprocessing

Biomarkers above are dependent on the quality of images taken from different modalities. A lot of work has been done by researchers since the last two decades to enhance the images quality so that the ophthalmologists can quickly determine abnormalities from them. The performance of DR detection

techniques depends on image processing algorithms like enhancement and segmentation of images [24] to extract useful information. These techniques are also utilized to enhance the visuals of images. Also, it is essential to improve low contrast data of retina blood vessels with respect to the background. Otherwise, it 's hard to extract the abnormalities. Some enhancement methods were used such as histogram equalization and other enhancement techniques to improve the contrast of images [17, 36]. Contrast stretching is one of the essential image enhancement techniques. Most common contrast stretching techniques are based on local and global contrast [46], partial contrast [23], bright and dark contrast [14]. Nowadays DR detection at the premature stage is a challenging area of medical image processing.

In the proposed system, two techniques namely CLAHE [50] and ICA [1] are utilized for local and global enhancement. CLAHE is a small window built method which is utilized to improve the distinction of retinal blood vessels with reference to its background keeping the bright and dark areas in perspective. It further improves the vessels in changing environment uniformly, and it is an extended technique of histogram equalization and contrast stretching [33]. The main reason of utilizing CLAHE is to apply it on small tiles obtained by dividing the image into small window's image. Grey level values are uniformly dispersed earlier inside the window to confirm an observable concealed structure. Mean filter using CLAHE is used to improve the fundus image. This identifies the vessel. Later, bottom-hat morphological transformation is applied to eliminate the retinal vasculature. Background noise elimination is done through contrast stretching to decrease surplus line structures.

Let $\phi_{d\min}$ and $\phi_{d\max}$ be termed as least and maximum intensity values that can be described mathematically as:

$$h = 255 * \frac{[\Theta_s(\phi_d) - \Theta_s(\phi_{d\min})]}{[\Theta_s(\phi_d \max) - \Theta_s(\phi_{d\min})]} \quad (1)$$

Where, Θ_s is known as sigmoid function and ϕ_d represents the dark or bright regions respectively. Sigmoid function Θ_s can be defined as:

$$\Theta_s(\phi_d) = \left[1 + \exp(\frac{\varpi_s - f}{\sigma_s})\right]^{-1} \quad (2)$$

Where, ϖ_s and σ_s represents the mean and variance of intensity values respectively.

ICA is a method to examine innovative signals from the combinations of numerous self-determining sources [11, 18]. Here low contrast enhancement in fundus image is done by ICA for retinal pigment structure, i.e., hemoglobin, muscular pigment, and melanin. Figure 2 shows the result of preprocessing fundus image.

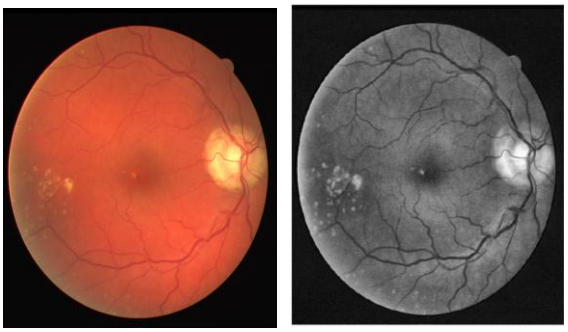


Figure 2. Candidate region preprocessing.

2.1.1. Vessel Extraction

After enhancement, next phase is to determine the blood vessels and eliminate it from the candidate region. It is a very sensitive process because it can eliminate or introduce clinical information that can be helpful or dangerous in clinical patient screening for DR grading. For this purpose, matched filter is applied that uses Gaussian curve [41]. Blood vessels contain low contrast intensity values which require extra enhancement. Consequently, a matching of 2-dimensional filer with the kernel is needed. This convolves the original image. It can be defined as:

$$I(u, v) = -\exp(-\frac{u^2}{2\sigma^2}), \text{ for}|v|<=L/2 \quad (3)$$

Here, L is the length of the segment along y-axis where vessels are considered to have constant orientation. Then the thresholding technique is employed to extract the blood vessels. Figure 3 depicts the outcomes of blood vessels recogonition.

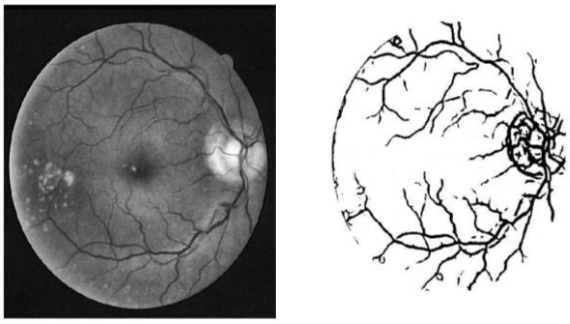


Figure 3. Preprocessed image and respective blood vascular pattern.

2.1.2. Optic Nerve and Macula Detection

The localization of retinal landmarks in particular Optic Nerve Disk (OND) plays an important role to correct pathological conditions of DR in the CAD system. The brightest region in the retinal fundus image is OND. OND contains three unique properties for its localization:

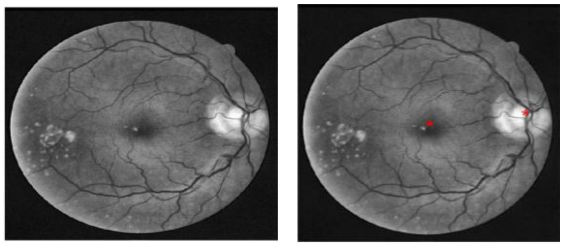
1. It appears as the highest intensity value having approximately 1600m in diameter.

2. Arteries and veins enter and leave from it.
3. Blood vessels also depart from here.

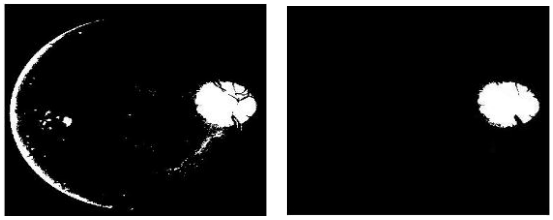
The following Equation calculates the central mass of OND:

$$x_i = \frac{\sum_{1}^{m} x_m}{m} \quad y_i = \frac{\sum_{1}^{n} y_n}{n} \tag{4}$$

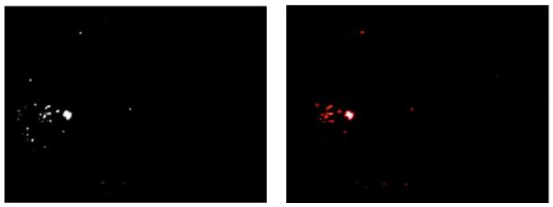
On the other hand, the macula is the darkest region located near to OND and approximately in the center of the retina. It is a sensitive retinal area and liable for thorough pivot vision. Classification related to retinal abnormalities is essential to identify the pivot region of macula which is known as the fovea. Much work has been carried out to identify the area of macula [26, 33]. In the proposed system, simple thresholding technique is extended to eliminate macula subtraction. Figure 4-a and Figure 4-b show the marked selection of OND and macula and segmentation of OND respectively.



a) Marked selection of macula and OND.



b) Segmentation of OND.



c) Lesion segmentation of candidate region in fundus image.

Figure 4. Optic nerve disk preprocessing,segmentation and lesion selection.

2.1.3. Lesion Segmentation

The key marks of NPDR are called Exudates. It is the ruling starting point of blindness. Early screening process helps to prevent this problem. The growth of protein and lipid in the retina create EXs which are white or cream color bright lesions [42]. Additional MAs is also the significant biomarkers of NPDR and is started by the principle dilatations of thin vessels of the blood. MAs are of minor dimensions, nearly red in color and round. The difference of MAs and HMAs is minor bright red dots and larger bright red dots respectively. In this paper, the first average threshold for N DR affected images is selected manually, and the algorithm successfully detected the biomarkers mentioned above. Then, the statistical CFT is utilized to compute the minimum intensity value for the detection of biomarkers. The CFT is defined as follows:

$$f(x) = p1 * x + p2 \tag{5}$$

Where x is the highest intensity in the processed image and-and $p2$ are the constant coefficients having 95% confidence boundary. The binary lesion segmentation for MAs, HMs, and EXs extracted from processed image is defined as:

$$I(x,y) = \begin{cases} 1, & I(x,y) > f(x) \\ 0, & I(x,y) < f(x) \end{cases} \tag{6}$$

Where, $I(x,y)$ is known as intensity value of fundus image. Figure 4-c shows the segmentation of lesion.

3. Feature Extraction and DR Grading

Normal, mild, moderate and severe DR is used by different works for automated classifications of fundus images [8]. Commonly, fundus images are further categorized by different authors into two, three, four and five classes. In a two class, the images are normal and NPDR whereas Normal, PDR, and NPDR are for three class classification. On the other hand, for four classes, the categories are normal, moderate NPDR, severe NPDR and PDR whereas normal, mild DR, moderate DR, severe DR and PDR are for five class classifications.

In this paper, four class classifications of fundus image are used which are normal, mild, moderate and severe DR. For the classes above; it is essential to extract significant features for accurate screening. In this regard, the candidate region is divided into three rectangular shape areas in the center of the macula. To form a feature set, the following feature set is ensemble for accurate classification.

- f1-f3: Calculations of mean, standard deviation and sum of each pixels values of every part.

$$f_1 = \sum_{i=1}^{N} I(x,y) \tag{7}$$

$$f_2 = \frac{f_1}{N} \tag{8}$$

$$f_3 = \frac{1}{N}\sqrt{\sum_{i=1}^{N}(I_i(x,y) - f_2)^2} \tag{9}$$

- f4-f6: Count number of EXs, H and MAs in each part.
- f7: Convert original fundus image into HSV color space and calculate the mean value from inside of candidate region.
- f8-f10: Sum of the difference of EXs, H, and MAs with a manually selected trained value of EXs, HMAs, and MAs from inside of candidate region.

- f11: Calculate the cross-bin distance from the average trained value of macula region. It can be defined as follows:

$$f_{11} = (h_{macula} - h_{avgTrained})^T W (h_{macula} - h_{avgTrained} \quad (10)$$

Where W=[x_{ij}] is the weight matrix and [x_{ij}] represents the similarities between bins.

Let F be the features set to represent the candidate region. It can be defined as:

$$F = \{f_1, f_2, f_3, ... f_n\}, \text{ where } n = 11 \quad (11)$$

Consider, C illustrates the class representation and $\{C_i \mid i = 1,2...n_C\} \in R^D$ is the i^{th} class where n_C shows the total number of classes.

Therefore in the first step, the data is classified into two stages which are normal and severe. Severe stage arises by the accumulation of exudates around macula region which is classified by using Gaussian Bayes classifier [39]. This classifier optimality detects the severe stage DR based on MAs and EXs. It can be written as:

$$p(c \mid y, X) = \frac{p(y \mid X, c) * p(c)}{p(y \mid X)} \quad (12)$$

Where, X represents the combination of f1-f6 input feature vector to classify the severe stage DR or non-severe stage DR, y represents the observed target value and $p(c)$ is known as prior class $p(y \mid X, c)$ which can be expressed as:

$$p(y \mid X, c) = \int p(y \mid X, c) p(c) d_c \quad (13)$$

Also, to observe severe stage of DR, the central part of candidate region is considered to be extracted based on the center of the macula.

Next, two methods namely multi-class Gaussian Bayes classifier and multi-SVM are used to classify other stages. Entire set of feature vector (f1-f11) determine the performance of both classifiers. In this paper, feature extraction is done manually for N training images.

4. Results

To perform quantitative and comparative analysis of DR grading, three different datasets are used namely Structured Analysis of Retina (STARE) [15], DIAbetic RETinopathy DataBase (DIARETDB1) [20], Digital Retinal Images for Vessel Extraction (DRIVE) and hospital database. STARE dataset contained 20 color images having a resolution of to 700×605 pixels, in which 10 images of them do not provide any pathology sign, taken by TopCon TRV-50 funds camera. While patients are aged between 25-90 years. DIARETDB1 dataset that includes 89 retinal images. These images have resolution of 1500X1152 pixels. Also they possess features related to noise and illumination. Moreover, in which five images considered do not pertain any DR lesions selected by medical experts and ground truth provided by an expert by soft map. DRIVE dataset compose of 400 diabetic images, patients aged between 25-90 years in which, 33 images do not have any sign of DR. Each retinal image is taken using Canon CR5 camera and having a resolution of 768×584 pixels. The Table 1 summarizes the comprehensive specifications of the selected datasets.

Table 1. In depth specifications of the selected datasets, IVW: Illumination variation within images; IVA: Illumination variation across images.

Specifications	STARE	DIARETDB1	DRIVE
Cameras	Fixed	Fixed	Fixed
FOV	35	50	45
IVW	Normal	High	Normal
IVA	Normal	Low	Normal
Image Resolution	Fixed	Fixed	Fixed
Mydriatic	No	No	No

Furthermore, we implemented our proposed algorithm on a Corei-5(2.3-GHz PC) with 4GB of RAM. Moreover, in terms of time complexity our models usually converge is less than in a minute to diagnose DR in each stage.

Fifty percent of the dataset is selected at random for training, and remaining half is randomly selected for the testing purpose. In addition, performance is measured by using Sensitivity (Sen), Specificity (Spec) and Accuracy (Acc), which are defined as:

$$Sen = \frac{TP}{TP + FN} \quad (14)$$

$$Spec = \frac{TN}{TN + FP} \quad (15)$$

$$Acc = \frac{(TP + TN)}{(TP + TN + FP + FN)} \quad (16)$$

Where TP,TN,FP,and FN to stand for True Positive, False Positive, True Negative and False Negative respectively.

For grading of normal and severe stages DR, the statistical information on databases is tested as follows:

$$I(x_m, y_m) = \begin{cases} Normal, & p < t \\ Sever, & p > t \end{cases} \quad (17)$$

Where, P is known as mean, standard deviation and sum of the macula region having $100*100$ region and t is the threshold. Equation (12) classifies all the information generated by Equation (17). The accuracy of classification results of normal to severe is up to 99% and 98% respectively.

Tables 2, 3, 4, and 5 show the analysis of three different databases.

Table 2. Performance evaluation of DR grading at the various stages on DRIVE dataset.

Stages	Multi-class Gaussian Bayes Exudates			Multi-class SVM Exudates		
	Sen%	Spec%	Acc%	Sen%	Spec%	Acc%
Normal	100	97	99	100	98	99
Mild	90	94	95	94	96	97
Moderate	89	97	96	92	95	96
Severe	99	96	97	99	97	98

Table 3. Performance evaluation of DR grading at different stages on DIARETDB1 dataset.

Stages	Multi-class Gaussian Bayes Exudates			Multi-class SVM Exudates		
	Sen%	Spec%	Acc%	Sen%	Spec%	Acc%
Normal	100	96	99	100	97	99
Mild	90	93	96	94	95	96
Moderate	89	95	97	91	94	96
Severe	99	95	96	99	97	98

Table 4. Performance evaluation of DR grading at different stages on Hospital database.

Stages	Multi-class Gaussian Bayes Exudates			Multi-class SVM Exudates		
	Sen%	Spec%	Acc%	Sen%	Spec%	Acc%
Normal	100	98	99	100	97	99
Mild	93	96	95	95	97	97
Moderate	91	97	96	92	95	96
Severe	96	98	98	99	98	98

Table 5. Performance evaluation of DR grading at different stages on STARE dataset.

Stages	Multi-class Gaussian Bayes Exudates			Multi-class SVM Exudates		
	Sen%	Spec%	Acc%	Sen%	Spec%	Acc%
Normal	100	97	99	100	97	99
Mild	90	93	96	93	95	96
Moderate	90	95	96	92	93	94
Severe	99	95	96	99	96	97

In the next experimentation, the proposed method is compared with the prevailing DR grading methods. Often the comparisons are complex because of the use of dissimilar frameworks by the researchers. The performance comparison clearly indicates that the presented architecture yields better results with respect to other existing methods for MA detection. Tables 6 and 7 show the assessment of our method on with prevailing methods for MA and EXs detection.

Table 6. Proposed method and other techniques for MAs performance comparison.

	Sen%	Spec%	Acc%
Akram *et al.* [2]	98.6	99.69	99.40
Niemeijer *et al.* [30]	100	87	-
Fleming *et al.* [7]	85.4	83.1	-
Walter *et al.* [47]	88.5	-	-
Keerthi *et al.* [19]	88.46	-	-
Larsen *et al.* [22]	71.4	96.7	82.6
Multi-class SVM	98.86	99.74	99.42
Multi-class Gaussian Bayes	95.1	97.3	97.60

Table 7. Proposed method and earlier techniques for EXs, a performance comparison.

	Sen%	Spec%	Acc%
Akram *et al.* [3]	97.39	98.02	97.56
Ranamuka and Meegama [35]	81.75	100.00	99.84
Sinthanayothin *et al.* [40]	88.5	99.7	-
Clara *et al.* [19]	90.2	90	-
Niemeijer *et al.* [30]	95.0	86.0	-
Osareh *et al.* [32]	93	94.1	93.4
Walter *et al.* [47]	92.74	100	96.7
Multi-class SVM	96.64	98.69	99.40
Multi-class Gaussian Bayes	95.8	98.3	97.60

The level lesion experiment on different datasets is performed further. Multi-class Gaussian Bayes classifier does this analysis. Tables 8 and 9 show the EXs and MAs classification results on various datasets. The results are obtained on deep pixels analysis of images. For Ex and MAs labeling, the deep pixels analysis is done through CFT and then multi-class Gaussian Bayes classifier is applied for dark and bright labeling. It is revealed from the analysis that EXs are more accurately detected than MAs.

Table 8. Performance evaluation of Exudates (EXs) on hospital database.

Database	Exudates (EXs)		
	Sen%	Spec%	Acc%
DB1	94	96	97
DB2	93	95	96
DB3	96	97	98

Table 9. Performance evaluation of MAs/ HMAs on hospital database.

Database	MAs/ HMAs)		
	Sen%	Spec%	Acc%
DB1	93	95	96
DB2	92	95	94
DB3	95	93	96

5. Conclusions

This research work proposes a preprocessing and feature extraction method to classify the DR at different stages. Preprocessing is an essential step at lesion level image segmentation for DR classification. CLAHE and ICA are combined for the preprocessing of retinal digital. Further, in the stat-of-art methods, Gaussian Curve Fitting technique is extended with thresholding technique for vessels extraction, ODN, and lesion detection. To strengthen the reliability, eleven different features are ensemble for the accurate classification of normal and abnormal retinal images. For classification purpose, multi-class Gaussian Bayes classifier and multi-SVM were used. The proposed approach is validated on two publically available databases namely STARE, DRIVE, DIARETDB1 and one hospital database collected by the authors. The average accuracy of both classifiers is better on normal to severe stages as compared to mild to moderate stages. Collectively results are shown in the results section.

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