Fundus Image Analysis to Detect Abnormalities in Diabetic Retinopathy using Computer Aided Design Tools - A Review

R. Lavanya, G. K. Rajini

Abstract: ***Diabetic retinopathy is becoming a major threat to visual loss in human beings. Many researchers are working to develop early detection techniques, which may reduce the risk of vision loss using image-processing techniques like image enhancement and segmentation. Improving the quality of medical images to detect the disease at an early stage is crucial for further medication. It is gaining more focus with automated techniques for machine learning. Filtering and morphological operators enhance image contrast and interested region can be extracted using segmentation techniques from the fundus image of the retina. For feature analysis the optical disk, localization of blood vessels and segmentation are very useful to observe the parameters like area, length and perimeter of blood vessels etc. Algorithms for this analysis include preprocessing, segmentation, feature extraction and classification. This paper tries to give a detailed review of various image-processing methods used in early detection of diabetic retinopathy and future insights to develop algorithms, which reduces clinician's time for diagnosis and pathogenesis.***

Keywords: Diabetic retinopathy, Image enhancement, Pre-processing, IRE, Microanueurysm, Segmentation, Feature Extraction, Machine learning.

I. INTRODUCTION

Diabetic Retinopathy (DR) can be classified into two types namely Proliferative and non-proliferative. Abnormal vessel growth (also known as neovascularization) in retina refers to Proliferative Diabetic Retinopathy (PDR). The early stage of the disease without neovascularization is referred as Non-Proliferative Diabetic Retinopathy (NPDR). As the disease progress, it may develop into PDR causing severe vision problems, sometimes leading to permanent vision loss too [1]. A high level of blood sugar (known as Hyperglycemia) in humans causes diabetic mellitus like damage to capillaries of the retina. Early signs of diabetic retinopathy are Microanueurysm (small outpunching of retinal capillaries). Microanueurysm rupture and form as hemorrhages inside the retina weakening the vessels and cause fluid to seep into the retina. Fluid deposits under the macula termed as macular edema, which interferes with the normal vision slowly turns into PDR. NPDR is further divided into Early NPDR and Moderate NPDR. At least one Microanueurysm (small outpunching's) present in the retinal exam it gives signs of early NPDR. If more Microanueurysm present, then cotton wool spots known as Moderate NPDR characterize it and it leads to severe NPDR with venous bleeding and severe Intra-Retinal Micro Vascular Abnormalities (IRMA). Leaking of serum proteins and fatty deposits sometimes appear as cluster of microanueurysm found yellow in color in fundus retinal images and are known as exudates. Accumulation of lipids and proteins in the retina is termed as exudates. So abnormalities in the retinal images include detecting exudates and neovascularization are the useful features for automatic detection. As NPDR progresses, to bypass the damaged vessels, new vessel growth starts which is known as neovascularization. These new vessels are leaky and tenuous or brittle and sometimes misdirected and grow towards the vitreous causing sudden vision loss. Fundoscopy or Ophthalmoscopy allows clinicians to examine the retina, the optic disk and the underlying layer of blood vessels. As the disease progress, the diabetic retinopathy may cause vision loss [1], hence detection at an early stage is crucial. Computer-aided design tools play the major role to detect abnormalities at an early stage and help clinicians for proper diagnosis and treatment within less time [2, 3]. This paper tries to review various methods in literature to detect abnormalities in diabetic retinopathy at an early stage with the help of image processing techniques automatically. The following Fig.1. shows the disease progression from normal retina to proliferative retinopathy.

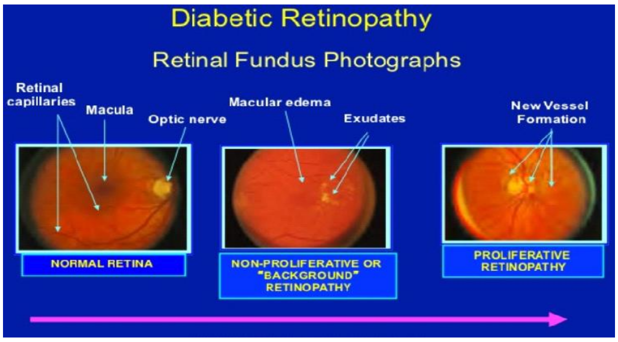

Fig. 1. Disease progression from the normal retina to the Diabetic retina

II. METHODOLOGY

Ophthalmoscopy or Fundoscopy is used to get the image of an eye in diabetic patients and these images are known as Fundus images. To get clear details of these, images are subjected to image processing techniques.

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In general, various image-processing techniques like image denoising [14], enhancement and segmentation techniques are used to detect abnormalities. Generally, the acquired or captured images are applied to pre-processing techniques to enhance the contrast, brightness of the images, then Interested Region Extraction (IRE) i.e either Microanueurysm or exudates are obtained through segmentation and classification techniques, or the abnormalities can be detected using machine learning algorithms. Predictive modelings is to simplify pathology with the automatic computer-aided diagnosis like pre-processing, segmentation, classification and feature extraction with machine learning and are very much useful in the detection of the disease at an early stage. The general procedure includes pre-processing the acquired fundus image for image enhancement, segmentation and feature extraction for classification to detect abnormalities is given below Fig. 2.

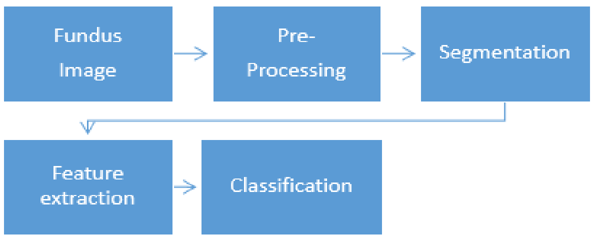

Fig. 2. General Flow of Retinal Image Analysis

Pre-Processing:

Retinal images from Fundoscopy are low contrast in nature and are not useful for detecting abnormalities by segmenting the selected or interested region. Generally available and most commonly used retinal databases are DRIVE (Digital Retinal Images for Vessel Extraction), STARE (Structured Analysis of Retina) DIARETDB (Diabetic Retinopathy Database), HRF (High-Resolution Fundus images database) and Messidor data sets. Fundus images are with poor contrast, non-uniform illumination, and noise. To increase the retinal image contrast, which is acquired from fundus camera many techniques are available in the literature, such as Local Histogram Equalization (LHE), Global Histogram Equalization (GHE) and Contrast Limited Adaptive Histogram Equalization (CLACHE). Pre-processing aims to highlight the interested region by enhancing the contrast. Various methods like spatial filtering techniques, which works on each pixel with different sizes of masks are available in literature. For enhancement, images from these databases are downscaled to overcome resolution and memory occupancy. Pre-processing steps include green channel extraction, downscaling and contrast enhancement making the image suitable for further processing. The accuracy of segmentation primarily relies on the consistency of the contrast of the entire image. Each pixel has its own importance for medical analysis, so without disturbing the image details contrast has to be increased. Many techniques have been proposed for enhancing low contrast images. Histogram Equalization has its simplicity and good performance in almost all types of images. Histogram Equalization is classified into two classes: Global Histogram Equalization (GHE) and Local Histogram Equalization (LHE) techniques are used to detect lesions of blood vessels and the presence of optic nerve in the image. Image enhancement techniques magnify the interested region and noise, which causes overshoots. To eliminate overshoots in Laplacian Operator, inverse diffusion equation is used along with self-similarity filtering [6]. Fig. 3 shows enhanced images of diabetic retinopathy with Microanueurysm, blood vessels, and exudates.

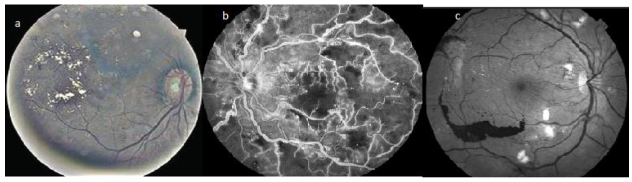

Fig. 3. Enhanced images of (a) Microanueurysm, (b) Blood vessels, & (c) Exudates

Denoising the image before segmentation tries to enhance the features at interested region and the performance metric used in pre-processing is mainly to calculate Peak Signal to Noise Ratio (PSNR) and entropy. Time Domain Constraint Estimator (TDCE) is used calculate the PSNR of the retinal image without losing any details of the retinal image. Intensity information of fundus image is enhanced using Singular Value Decomposition (SVD) with help of sub bands of discrete wavelet transform [8], where it calculates entropy as the performance metric and compared with other methods like LHE, GHE, and SVE (Singular Values Equalization). DREAM tries to check the severity in the disease with pre-processing techniques to separate foreground from the retinal image, which consists of candidates or features to observe the severity of the disease [53] with help of spatial filtering to enhance the image. This paper mainly worked on reducing the selected features. In the pre-processing stage acquired images from fundus photography are resized to 256 X 256 or 512 X 512 and the green channel is extracted for more information and to make it clear for further processing.

Morphological operator Dilation is applied on the green channel and Contrast Limited Adaptive Histogram equalization (CLACHE) is used to enhance the image. In this paper, pre-processing includes green channel extraction, morphological processing, and contrast enhancement achieved through CLACHE [84]. To get the final pre-processed image, CLAHE image is subtracted from Gray image. Multi score second order Gaussian filters are used to enhance the vessels in pre-processing. As vessels are tiny structures, to get greater enhancement [37] uses Left Invariant rotating Derivative frame [LID], and Locally Adaptive Derivative frame [LAD] are used. The following table gives literature survey on preprocessing for enhancement.

A. Segmentation

Segmentation is a process of subdividing the image into multiple segments as the sets of pixels or super pixels to analyze in computer vision applications. Segmentation is classified into three categories namely Supervised, Unsupervised and Semi-supervised. Supervised segmentation uses priori knowledge whereas unsupervised tries to find patterns of values and to build a probabilistic model to identify

Table- I: Literature survey on pre-processing for image enhancement

Image enhancement	Database	Method	Comments
Satyardi[3],[6]	DRIVE, STARE	Filter based technique's, Gaussian Intensity distribution,	Improves contrast, loss of some image details
Reza et al,[5]	DRIVE, STARE	Adaptive histogram	Improves local contrast as well as noise.
T.Jintasuttisak, S.Intajag [10]	DRIVE, STARE	Histogram-based	Improves contrast of the Green channel, Non-uniform Illumination, amplifies noise too.
Lavanya[13]	DRIVE	Cache filter	Improves tiny structures, computational complexity
Xue et al,[7]	DRIVE, STARE,	Gradient map & (LoG) Laplacian of Gaussian	Local contrast features extracted with phase Congruency
Sarath Chandra[9]	DRIVE, STARE, Pvt. Database	Histogram-based, Contour let transform	Improved PSNR
Miao et.al[11]	DRIVE, STARE	Multiscale top hat transformation, and linear stretching	Improved contrast in two levels, by extracting bright features and optimized
Xiao[12]	DRIVE, Pvt Database	Gamma correction	Gray levels of the green channel are extracted, the global contrast of the image is improved.

The substructures of the interested region in image analysis. Semi-supervised segmentation uses both labeled and unlabeled images of interested regions to identify abnormalities. In Diabetic Retinopathy, IRE may be Microanueurysm (MAs), Exudates (EXs) or Blood Vessels (BVs) and are application oriented.

Segmentation techniques are broadly classified based on an application, as if segmentation based on discontinuities (edge detection), or similarities (finding distance between the similar intensity pixels through connectivity based) using threshold based techniques. Segmentation methods are broadly categorized based on kernels, vessel tracking, thresholding, mathematical morphology and machine learning based [33, 41]. In segmentation process, Kirsch method applied for edge detection, which uses structuring element to find edges through neighbors. As each and every pixel is important to analyze medical images, for post-processing, dilation and erosion applied on segmented images to avoid the false detection of pixels. For retinal image analysis main features used to observe the abnormality are Exudates, Microanueurysm detection and blood vessel detection play crucial role in early detection of the disease.

(a) Microanueurysm (MAs): Microanueurysm is the first sign of visual impairments [16-26], detection of these is a trivial task which is close to blood vessels. Microanueurysm are focal dilatations of retinal capillaries with 10 to 100micro meters. Microanueurysm detection is obtained by calculating size, height, and shape of the peak with a directional cross-sectional profile centered on the local maximum pixel.

Multiscale correlation with dynamic thresholding is used to detect MAs at coarse and fine levels to get candidate selection and true MAs [17]. SVD with contrast enhancement is applied on fundus images and the Hessian-based approach is used for candidate selection. Radon transforms with intensity normalization and SURF are used to locate the exact MAs candidate region [18]. Kernel-based techniques use the concept of vessel profile with intensity variations and also termed as matched filter techniques [13]. The performance metrics are specificity and sensitivity are achieved up to 98.11% and 97.22 % with the confidence level of 0.75. Two types of segmentation methods are used to detect Microanueurysm effectively. They are coarse segmentation using morphological operators and fine segmentation with a Bayes classifier and achieved good results with 99. 9% accuracy. Locally matching lesion templates are used to detect Microanueurysm from the sub-bands of wavelet-transformed images [19, 25]. The wavelet transform used for MAs detection, here templates are used to match lesions locally from the wavelet sub bands [57, 59]. 90.44% sensitivity is achieved with Genetic algorithm as an optimization technique to select prominent features, which are used to observe abnormality in the given image. [20].

(c)Exudates (Exs): To get effective Exudate detection [28-35] Optical disc in the retinal image has to be eliminated using image segmentation. In paper [30] Exudate detection is achieved with an efficient integrated approach. The methodology includes various steps, first by enhancing the retinal image using Contrast Limited Adaptive Histogram Equalization, and then Hessian filtering separates blood vessels and the optical disk is identified with the combination of multiresolution analysis. In the remaining image fuzzy K-means, clustering is applied to detect exudates. K means clustering needs to specify the number of clusters and its effectiveness increases with maximum clusters, which in turn increases computational complexity. Exudates with the small radius are very hard to find, so Kirsch method tries to explore the edges in the retinal image. Linde-Buzo-Gray clustering is an improved version of K means algorithm by deriving good codebook for features, which detects the exudates by splitting the clusters but need improvements to find the location of cluster center [33]. This paper finds the bright lesions but fails to identify exudates with a small radius. Retinal image is pre-processed to improve accuracy in exudates detection, Exudate candidate regions are extracted with help of weighted ensembles, and these weights are determined using simulated annealing [34]. A novel approach proposed to get accurate borders of exudates, and exudates are identified using active contour method with the help of grey scale morphology and region wise classifier [35]. (b) Blood Vessels ((BVs): The structural details of blood vessels give maximum information to detect abnormalities in fundus images computer-aided tools. To detect vascular changes in blood vessels, vessels classified into arteries, veins and in turn graph based labels assigned to each vessel segment with the set of intensity features [38, 69].

By computing the geometric mean of the grey image of the diabetic retina, vessel orientation selectivity is achieved from the combination of difference Gaussian filters with unsupervised segmentation of blood vessels. For vessel detection, gradient is computed using different masks like Roberts, Prewitt, and Sobel operators. To describe global vascular structures of retinal blood vessels, intensity-based local features are employed to select the most prominent features with Expectation–Maximization optimization technique. For blood vessel segmentation Matched filter and fuzzy K , and median filters are deployed, and 96.43% sensitivity 76.31% specificity are achieved. Some researchers used Gaussian Intensity Distribution method for vessel segmentation. Blood vessel segmentation achieved with 94% accuracy, 69% sensitivity and 97% specificity using morphological opening and binarization. Optical disc segmentation is achieved using domain knowledge with the low-rank representation of super pixels, and these methods employed for clustering. A new automated method developed to detect blood vessels, which uses directional differential operators to extract the skeleton of main vessel and vessel direction is emphasized using multi directional top-hat operator with rotating structuring element. The vessel information extracted with bit plane slicing and this information is integrated with main skeleton by applying morphological filters and iterative region growing method [86]. To detect the blood vessels, in pre-processing CLACHE algorithm and 2D Gabor filter with morphological reconstruction are used to achieve an average accuracy of 95%. The multi-resolution analysis provides clear details of local binary patterns for texture analysis of blood vessels, which are also termed as uniform with computational simplicity [57]. Images are labeled on four-grade scale and features are extracted by isolating blood vessels, Microanueurysm and hard exudates using SVM to obtain 95% sensitivity. To extract local details with more features from the non-diseased fundus image and these features must be invariant to illumination changes and orientation of pixels. These extracted features from normal image are matched with diseased fundus image to detect abnormalities. Scale Invariant Feature Transform (SIFT) is a local descriptor which uses grey scale images for local information based on scale pace [82]. The following Fig.4 represents segmentation of (MAs (a), EXs (b) and BVs(c).

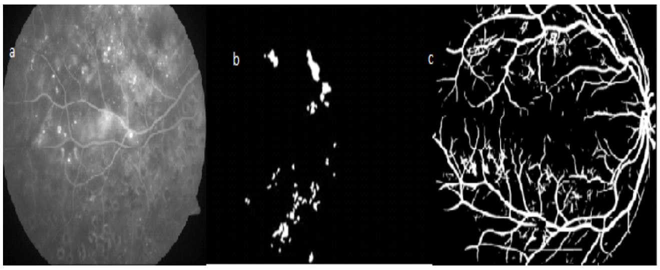

Fig. 4. Enhanced images of (a) Microanueurysm, (b) Blood vessels, & (c) Exudates

B. Feature extraction

Feature is a general term given for an interested region depending on the application used to develop subsequent algorithm and repeatability, robustness, discriminating and independence are its main characteristics. Combination of features forms feature vectors, which were used to encode the image information. The feature vector includes the statistical parameters like entropy, homogeneity, and Euler number etc., with 64-point DCT [35]. Various features currently used in the literature are shape, color, textural and histogram of an image. As per the abstraction level, they categorized into pixel based, local or global based of an image. [60]. Feature extraction is a process of quantifying the actual information to the desired level and making it adaptable for further processing like classification and detection of abnormalities in the original image for analysis purpose. Feature extraction involves both identifications of relevant features and their selection. To get accuracy in findings, there is a great impact in the selection of local and global features from the image. Shape features are the area, perimeter, thinness ratio, aspect ratio, compactness ratio and elongation or eccentricity ratio. Color features give the contrast details of individual primary colors of Red, Green, and Blue. Histogram features give details of intensity levels of the entire image and their distribution. From the histogram, the following parameters like mean, standard deviation, skewness, energy, and entropy can be computed. Fourier descriptors give spectral details of an image and the parameter power is the primary metric for spectral features. Spectral features used to obtain textural details of the image and are of the function of image size related to the interested region. The texture of interested region has a significant role in medical image analysis and it can be categorized with the use of statistical methods depending on first and second order details like mean, variance, standard deviation, skewness and central moments etc., whereas the first order statistical details can be obtained from histograms. Second order details like correlation, homogeneity, energy and central moments obtained from Gray level co-occurrence matrix and Gray level Difference matrix. These are explained by Haralick to analyze the medical images [54]. Local Binary Pattern (LBP) is very much useful for spectral components and it is invariant texture analysis [59]. Model-based methods try to extract textural features through spatial properties to find the spatial relationships of textural features by using Markov models or Gibbs random models or Gaussian random models [65]. Texture analysis gives a reasonable amount of interested region to identify the abnormalities [53, 55, 57, and 58]. For vessel segmentation, the main categories are filter bank based methods, multiresolution analysis; Gabor filters [23] and Gabor wavelets. Among all Gabor and wavelets provides better information. Filter bank based methods works in frequency and spatial domains by using image transforms [38, 58]. Real-time applications need both frequency and spatial information, so wavelet methods are very much useful [20]. Multiple features may give robust results based on regional characteristics like regional variance, regional gradient, and regional spatial frequency, which explains using the Shearlet transform with the help of sub band coefficients [72, 79 & 82]. While selecting features to classify an image, quality of features and interdependencies between features has gained importance [81, 83 & 85].

Speeded Up Robust Features (SURF) are the framework of multiple scale analysis using convolution and local gradient [84] to extracts low level or local features like intensity and orientation [82]. This paper proposed a new ranking method SVM-RFE to observe quality with a reduced computational time with simple distance transform to estimate vessel width as small, medium and large for feature extraction and global intensity information are calculated using statistical measures.

Classification

Classification of retinal images to detect abnormalities is carried out using various classifiers. In supervised learning, the main classifiers are logistic regression and Naive bayes classifiers are linear models, which work with more independent variables. In medical images ground truth images are used to train the classifiers, whereas in unsupervised no ground truth images are available [78]. The main classification algorithms are the nearest neighbor, K-nearest neighbor, nearest centroid, template matching, Bayesian analysis and Neural based. Decision tree classifiers are non-parametric in nature and selection of a suitable classifier improves the classification accuracy. Knowledge-based classification plays a crucial role in medical imaging. The cost function is the measure observing the success rate of classification algorithms. In retinal image classification mostly used cost functions are Specificity (Sp), Sensitivity (Sn), Precision, Accuracy, and F-measure. Table.2 gives different types of supervised and unsupervised classifiers used for retinal image analysis.

Table- II: Types of Classifiers

S.No	Supervised	Un-Supervised
1	Linear Classifiers	Markov random Models
2	Random Forest method	Pattern analysis
3	Support Vector Machine	Fuzzy Clustering
4	Decision Trees	Hierarchical Clustering
5	Gaussian Mixture models	K-means Clustering

It is always good to have ground truth images properly labeled by the clinicians which are used to train the classifier to get good results, like supervised vector machines (SVM), K-means classifiers, GMM models and Ad boost , Nearest neighbors, neural networks, random forest, decision trees and SVM [65] are mostly used classifiers. Many researchers worked on SVM, which outperforms among all the classifiers. Some researchers used neural networks for classification and Bayesian models too. Fuzzy C Means (FCM) clustering and SVM classifier is used to detect Diabetic Retinopathy and achieved Specificity of 95.83%, accuracy of 96.7% with a sensitivity of 100%. For binarizing input retina image line tracking concept is used and a hybrid technique with a combination of Scanning window analysis and Morphology is applied to get reliable results [33]. Neural networks are used for pixel classification and to detect Microanueurysm log Gabor features and Dual-Tree Complex Wavelet Transform are applied, then image feature is extracted by observing the difference between the intensity levels of the pixel with the pixel at the interested region [32]. This paper explains the local descriptors efficiently and termed as Local Contrast and Ordering (LCO) with higher computational efficiency. In neural networks, features of fundus image are applied as inputs to the number layers and network performance can be increased with a number of inputs, which increases computational cost, hence normalized inputs are used with iterative methods to reduce complexity in the network layers [62].

Multilayer Perceptron Neural Network [MLPNN], is used as a classifier which outperforms and achieves 100% training and cross-validation rates to detect abnormalities in the given image.. Pixel-wise classification is used to identify the maximum number of features from the vessels and the Genetic algorithm is used to optimize the features and achieved an accuracy of 90.2%, sensitivity of 89.6% and specificity of 91.3% respectively [40].

Residual Networks (ResNets) are gaining popularity with minimum feature vectors and little complexity to get better segmentation results. Residual Fully Convolutional Network is proposed to predict segmentation by normalizing medical images with Fully Convolutional networks (FCN)[49], and they iteratively refined. Deep learning [75, 76 & 77] methods are useful for supervised segmentation for retinal blood vessels and an accuracy of 99% and sensitivity of 87% are achieved. Hidden Markov models are an approach to trace the vessels accurately and occlusion handling [50]. The vessels are traced with an accuracy of 95.7% and specificity of 81%. To diagnose PDR, matched filter and modified local entropy thresholding is applied to extract the blood vessels by achieving an average accuracy of 97.6% with Extreme Learning Machine [87]. Enhance K means algorithm is used for blood vessel segmentation and vessel features are extracted with the help of ROI based LBP method. The extracted features were classified by Echo State Neural Network & RBF and achieved an accuracy of 97.95% [88]. To observe global features of an image, histograms are very much useful and sometimes, Histogram distribution of different pixel class overlaps each other, which makes estimation of global parameters inaccurate. Estimation of local parameters with high accuracy is difficult due to inhomogeneity at different regions on spatial scale. To overcome this new method developed to calculate global parameters accurately [89]. One such method is Slope difference distribution for histogram is calculated and then global peaks identified. The local parameters calculated using Gibb's distribution, which characterizes image as markov model with joint distribution function and achieved good segmentation accuracy with an error rate of 5.7431 when compared to K-means 7.8177. The following Tables 3 and 4 summarizes literature review about various methods used for the analysis of abnormalities in Blood vessels (BV), Exudates (Ex) and Microanueurysm (MA).

Table III Various approaches in segmentation procedures

Paper	Author & Year	Abnormalities			Database	Method	Performance Metrics		
							Acc	Sp	Sn
Machine learning approach for exudate	Akara.Sophark 2010	MA	Ex	BV	N.A	Naive Bays+ SVM	98.14	92.28	98.52
Automatic Exudate detection	B.Harangi et.al 2012	-	-	Yes	Diaret DB1	Active contour, region wise classifier	NA	NA	NA
Automatic Exudate detection	Wuttichai Laungruang,2014	Yes	Yes	Yes	DIARE TDB	Hessian filtering, Fuzzy c means	NA	NA	NA
Retinal vessel segmentation with ELM	C.Zhu.et al 2017	Yes	Yes	Yes	DRIVE	Phase Congruency & ELM classifier	96.07	98.68	71.4
DREAM	Sohini Choudhury 2014	Yes	Yes	Yes	DRIVE, STARE	-	90	50	100
Optimum Wavelet Transform	G.W name et.al, 2008	Yes	Yes	Yes	Pvt.Database	Wavelets Genetic algorithm	--	--	89.92

Table IV various approaches in segmentation procedures

Paper	Author & Year	Abnormalities			Database	Method	Performance Metrics		
		MA	Ex	BV			Acc	Sp	Sn
Robust hidden Markov model-based intelligent Blood vessel detection	Hassan.M.et al, 2017	-	-	Yes	DRIVE	Hidden Markov models	95.7	81	97
Automatic Detection O Microanueurysm and Haemorrhage's in Colour Eye fundus images	Sérgio Bortolin Júnior and Daniel Welfer	Yes	Yes	Yes	NA	CLACHE	92	--	87.6
Blood vessel segmentation in colour fundus images based on regional and Hessian features	Shah SAA, Tang TB, Faye I, Laude A	Yes	Yes	Yes	DRIVE	CLACHE, B-COSFIRE	94.7	--	72.5
Analysis of Retinal Vasculature using a Multiresolution Hermite-Gaussian Model	Li.wang, Abhir Bhale Rao	Yes	Yes	Yes		Morphological operators	97	92	76
Exudate detection in colour retinal images for mass screening of diabetic retinopathy	Xiwei Zhang 2014	Yes	Yes	Yes	E-OpthaEx	Morphology & Random forest	97	93	78

III. CONCLUSIONS

This paper explores various image processing techniques and machine learning algorithms for detecting retinal abnormalities like the growth of abnormal vessels from normal vasculature, small Microanueurysm, and exudates, which may lead to permanent vision loss. Many researchers worked on pre-processing techniques to brighten the retinal structure for visual quality; still there is an ambiguity in standardizing the methodology to be followed.

As per the state of art, CLACHE technique outperforms in the pre-processing stage to improve contrast details, but a small amount of noise gets amplified and which is not recommended. In the segmentation process, the combination of connectivity based and thresholding techniques outperform with more complexity. In few papers, for classification of abnormality in the diabetic retinal images around 30 to 40 intensity, textural and statistical features observed for proper detection and there are no specific criteria for selecting a number of features to train the classifier. Some researchers used the maximum number of features with optimization techniques to obtain greater accuracy. Still, more work is needed to reduce the number of features to be used and to observe their effectiveness. The genetic algorithm used to optimize the number of features extracted and it is observed that instead of a single classifier, cascaded classifiers and semi-supervised learning outperforms for the given application. Now a day's deep learning, which is a subfield of machine learning, has been emerging as a prominent research area in retinal image analysis due to its effectiveness and less computational complexity. Still, improvements are needed to have accurate algorithms. Microanueurysm detection, Artery and vein classification of retinal images from fundus photography are giving more scope for future directions with proper selection of robust classifiers with suitable segmentation algorithm for computer-aided design. Hybrid methods like pixel-based segmentation with morphological operators are giving better results. This paper may give selection criteria for further research in retinal image analysis.

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It is optional. The preferred spelling of the word "acknowledgment" in American English is without an "e" after the "g." Use the singular heading even if you have many acknowledgments. Avoid expressions such as "One of us (S.B.A.) would like to thank ... ." Instead, write "F. A. Author thanks " *Sponsor and financial support acknowledgments are placed in the unnumbered footnote on the first page*.

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