Automatic Diagnosis of Diabetic Retinopathy using Machine Learning: A Review

Piumi Liyana Gunawardhana
Faculty of Information Technology
University of Moratuwa
piumihansika94.phlg@gmail.com

Raviru Jayathilake
Faculty of Information Technology
University of Moratuwa
raviru18@gmail.com

Yasiru Withanage
Faculty of Information Technology
University of Moratuwa
withanageyasiru@gmail.com

Gamage Upeksha Ganegoda
Faculty of Information Technology
University of Moratuwa
upekshag@uom.lk

***Abstract*— Diabetic Retinopathy is a popular cause of diabetes, causing vision-impacting lesions of the retina. Blindness may be avoided by early detection. The ophthalmologist's manual approach of diagnosing diabetic retinopathy is expensive and time consuming. At the same time, unlike computer assisted diagnostic systems, it may cause misdiagnosis. Deep learning has recently become one of the most effective approaches that has obtained better efficiency in the analysis and classification of medical images. In medical image analysis, convolutional neural networks are more commonly used as a deep learning approach and they are extremely effective. This paper assessed and addressed the new state-of-the-art Diabetic Retinopathy color fundus image classification and detection methodologies using deep learning and machine learning techniques. Additionally, various challenging issues that need further study are also discussed.**

Keywords— Diabetic Retinopathy, Deep Neural Network, Convolutional Neural Network, Retinal fundus images, Machine Learning

I. INTRODUCTION

Diabetes is a condition that is widespread worldwide and can cause severe microvascular complications. This disease's prevalence has doubled over the past thirty years, and is expected to only increase, particularly in Asia. About one-third of people with diabetes are likely to be diagnosed with diabetic retinopathy (DR), a progressive eye condition that may lead to permanent loss of vision. The retinal images are the most used method of screening due to its high sensitivity to retinopathy detection. Early identification, which is vital to successful prognosis, depends on skilled readers and is time-consuming as well as labor consuming [1]. It creates a dilemma in places where skilled healthcare services are generally not accessed.

These problems can be alleviated with an automated system, either as aid for medical professionals' work or as a full screening tool. In detecting referable diabetic retinopathy, known as moderate or worse diabetic retinopathy, a deep learning artificial neural network-based automated system approach may obtain optimal sensitivity with higher sensitivity [2].

This paper critically reviews the existing methodologies in the literature about automatic DR diagnosis using Machine Learning (ML), Deep Neural Networks (DNN), and Convolutional Neural Networks (CNN) techniques, retinal fundus image pre-processing techniques and briefly explains the background, features and symptoms of DR.

Paper is organized as follows: Section 2 briefly explains the background, features, and stages of DR, while Section 3 presents the various pre-processing techniques and approaches that can be applied to colour retinal fundus images. Section 4 presents knowledge base approaches in literature to diagnose DR while Section 5 presents the conclusion.

II. BACKGROUND AND FEATURES

Much of the patients were in a critical and advanced stage when DR was first identified, which was difficult to treat. Early diagnosis of DR is basically known to be crucial for good prognosis since the tests and therapies are being examined and improved, and the prognosis of the patient can be raised by a large percentage if microaneurysms can be better diagnosed at the earlier level. Screening is used in the advancement of technology to detect defects in the retina. Researchers have found that for higher-risk patients, scanning eyes by fundoscopy has decreased the risk of making them fully blind from DR [3]. Fundoscopy clinical findings diagnosis, a diagnostic technique for observing the eye, depends on a broad variety of image features and locations. For patients with early stage DR, diagnosis is extremely difficult, as this relies, among several other characteristics, on the discernment of the presence of microaneurysms, mild saccular outpouching of blood vessels, retinal hemorrhages, ruptured vessels in fundoscopic images. In fact, fundoscopy images offer detailed images that promote early-stage DR diagnosis.

According to an international classification of DR levels of s eriousness, the diabetic retinopathy phases include [4]:

1. No DR (R0): The eye is unaffected by the disease at this stage.

2. Mild DR (R1): during the first phase, mild nonproliferative, balloon-like inflammation can occur in small regions of the retina's blood vessels.

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3. Moderate DR (R2): A several blood vessels in the retina can get blocked in the second phase, known as moderate no proliferative retinopathy.

4. Extreme DR (R3): Extreme nonproliferative retinopathy in the third phase progresses to more blocked blood vessels, resulting in regions of the retina no longer getting sufficient blood flow. The retina cannot build new blood vessels to repair the lost ones without sufficient blood circulation.

5. Proliferative DR (R4): Proliferative retinopathy is known as the fourth and final phase. This is the disease 's critical phase. In the retina, other abnormal blood vessels will start growing, but they will be delicate and weak [3], [5]. Figure 1 depicts the color retinal fundus images of eyes with DR and without DR.

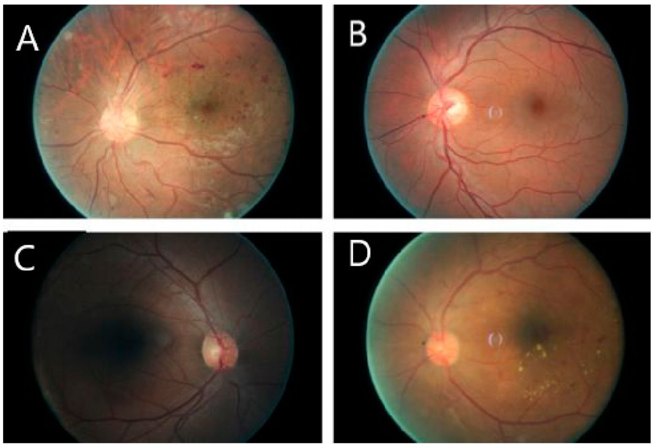

Figure 1 . Sample frames of the retina images. A, B frames in the top row come from normal subjects, while the C, D in the bottom row come from the patients who have DR.

Microaneurysm (MA) is the earliest feature which can be identified in DR. Small circular items with dark red spots are MA. A growing amount of microaneurysm can contribute to the development of retinal ischemia and retinopathy. Further, to wake the vessel wall, microaneurysms can cause retina blood vessel obstruction. These microaneurysms can rupture, causing bleeding to occur. MA are characteristics that can often be seen or observed in the early stages of DR, according to a global classification of DR levels of seriousness, while hemorrhages (HEM) can be seen in more advanced phases [4].

HEM will be the next DR complication that induces strain in the vessels that contributes to the middle of the eye leakage of a gel type material. The contamination of weak vessels triggers HEM mainly [6]. Like the MA, HEM is also in the form of a varied thickness and non - linear margin red spot. HEM is traditionally divided into two categories: flame and dot-blot HEM (DBH), arising from the precapillary arterioles in the first category and emerging from the nerve fibers [4]. Compared to MA, the DBHs are circular and lower on the other hand. At various stages of the retina, DBHs can appear and can happen at the venous end of the blood vessels [7].

NPDR is the first step of the expansion of blood vessels and fluids that leak into the retina that could contribute to visual impairment. NPDR can be divided into three phases according to its severity: mild, moderate, severe [4].

PDR is simply the development of new capillaries in the eye and hemorrhage, which threatens the retina and other areas of the eye. The more severe type of DR is known as (PDR) Proliferative DR. This triggers many vision issues and may lead to total loss of vision [4], [6].

Hard exudates (HE) are yellowish, asymmetrical in shape and glossy, the third DR symptom. The third DR symptom that is yellowish, asymmetrical in structure and glossy is Hard Exudates (HE)[4], [6] . HE can emerge within the retina, which causes lipoproteins and proteins to release out of the retinal blood vessels, unlike MA[6] . HEs typically take the shape of a round ring adjacent to the MA and appear to be in the external retina layer.

III. Pre-Processing

Image preprocessing is a crucial task in eliminating noise from images, improving image visual features, and maintaining image quality. The following paragraphs analyze the most prevalent and popular pre - processing techniques that have lately been used in research [7] .

A. Cropping and Resizing

The preprocessing consists of images being cropped, accompanied by resizing them. To be suitable for the network used, the images were resized to a fixed resolution by several researchers. To eliminate the unnecessary regions of the image, cropped images were used. Then the images were normalized by data normalization into a similar distribution [8]. Dilip Singh Sisodia et al. standardized them, as the data set images vary significantly in size and some images are trimmed at the top and bottom. Since an image's field of view (FOV) (the portion of the retina shown in the image) is circular and cropped first to a side square equal to the FOV 's diameter [5]. Using Otsu 's method to extract the circular colored image of the retina, Fatma A. Hashim et al. cropped the images. Images were normalized by subtracting the minimal pixel intensity of each color channel and dividing them by the mean pixel intensity to reflect pixels in the 0 to 1 range. Every cropped image was resized by Jaakko Silsden et al. to five different standard input image sizes. The biggest image size was the lowest native resolution of the retinal images after the preprocessing steps. The creation of various resolutions was carried out in order to analyze the impact of the input image resolution on the classification results. [2].

B. Color channel

Three color channels are there in the color retinal fundus images: Red, Green and Blue (RGB). The red channel is brighter and has the highest luminosity where the Optic Disk (OD) can be seen in a clearly defined manner [5]. The green channel has the highest contrast, while the blue channel is empty. Contrast normalization is generally applied on the "green" channel as it is less susceptible to noise. In all three channels, contrast enhancement was suggested by 3D histogram equalization or independent normalization of each channel. Figure 2 shows the extraction of the green channel from color retinal fundus images, the channel where features can be clearly seen.

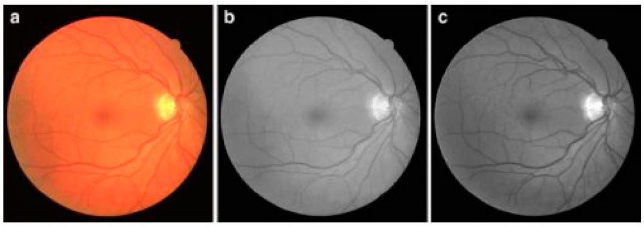

Figure 2. Results of separation of the red and green color channels from the full-color fundus image.
a- Color retinal image, b- Gray-scale image, c- Green-channel image

Due to its high contrast, only the green channel of the images was extracted in most of the works and the images were transformed to grayscale. [8]. The contrast is between the blood vessels, exudates, and hemorrhages, seen at its best in the green channel and this channel is also not poorly illuminated nor excessively saturated like the other two. Therefore, only the green channel was taken for evaluation and classification by Dilip Singh Sisodia et al. [5]. In the methodology by N.M. Salem et al. an improved intensity channel was suggested by mixing red and green channel data using histogram matching while the histogram stretched on the green component addressed by P. Feng et al. [9]. An intensity component that merges red and green Intensities was proposed by S. Lu et al. to get a modified channel that incorporates both characteristics, Fatma A. Hashim et al. suggest a move to measure an intensity component from both red and green intensities. As the variations of the blood vessels around the OD must be suppressed; it was done by assigning the red channel values a higher weight. At the very same time, the variance around the OD boundary must be maintained, that is achieved by assigning the green channel a lower weight [9].

C. Noise removal methods

The methods of noise reduction include the median filter, the Gaussian filter, and the Nonlocal Means Denoising method [8]. Reverse filtering is a kind of technique of restoration. If an image is distorted after using a particular filter, the original image can be restored using Inverse Filtering. Wiener filtering is a trade-off between the strategy of inverse filtering and sound smoothing. When a color fundus image is passed as an input to the Wiener filter, it eliminates the noise and obscuring properties and effects in the fundus image. The channel has maximum trade off taken as an input image. The median filter is generally used for salt and pepper noise reduction. The median is the neighborhood pixel's middle value, which is stronger than the mean filter. Median filters, while eliminating noise, preserve the sharpness of the image's edges. The downside of median filtering is that it omits all sounds and data. The pixel in the picture is classified by the surrounding pixel of the neighbor in the case of adaptive median filtering and the size of the neighbor is adjustable. Distortions and unnecessary boundary thickening and thinning are reduced by the adaptive median filter. Gaussian Smoothing executes the average value of neighboring pixels based on the Gaussian function. This operator reduces the distracting effects and other lighting. The low-pass Gaussian filter removes high-frequency components from the picture [7].

D. Data augmentation

Where certain image classes were imbalanced or to expand the number of the dataset, data augmentation techniques were conducted. Translation, rotation, shearing, tossing, contrast scaling and resizing are part of the data augmentation process. [8]. To enhance network localization capacity and minimize overfitting, Carson Lam et al. expanded the number of images in real-time. A random increase of images preserving collinearity and distance ratios was conducted at each epoch. With zeros, zoom, rolling and rotation, they introduced random padding. When applied to disease class Mild DR (R1), that is the most challenging to grade and the least in number, these affine transformations are especially efficient. The enhanced the 3-ary classifier sensitivity for the mild class from 0 to 29.4%, while this measure was nearly the same for the other two classes which are Moderate DR (R2) and Extreme DR (R3). After following the pre-processing steps, the 3-ary classifier achieves sensitivities for no DR (R0) and severe DR (R5) of 85% and 75% respectively as well as 29% mild class (R1) sensitivity. Given the drastic increase in measurement for the mild class (R1), even with 5% of the amount of data, it is obvious that data accuracy has a strong effect on the efficiency of the multi-class training model.

E. Contrast Enhancement

The efficiency of DR detection methods relies on image processing. Algorithms including image enhancement and segmentation to extract useful data. Such techniques are also used to improve the visual content of images. In addition, low contrast data of retina blood vessels about the context must be enhanced [3]. Otherwise, the abnormalities are impossible to extract. To increase the contrast of images, certain enhancement techniques such as histogram equalization and Other essential enhancement techniques such as contrast stretching were used [3], [5].

A method to resolve the decrease in contrast that happens when the distance of a pixel from the center of the image increases and to normalize the mean intensity was proposed by Santhinatha et al. First, the intensities of the three-color bands are converted to the representation of intensity-hue saturation; this is to increase the intensity contrast without impacting the relative pixel color values [9]. Figure 3 represents two color retinal images before and after contrast enhancement.

An adaptive transition is then introduced to increase the contrast [9]. Carson Lam et al. conducted contrast adjustment using the filtering algorithm for contrast limited adaptive histogram equalization (CLAHE). Dilip Singh Sisodia et al. split the image into smaller blocks and equalization of the histogram is performed. [5].

As a preprocessing phase for vessel segmentation, Salem N. et al. used histogram matching between the red and green planes. This enhances the differentiation of gross dark features like vessels but removes the contrast between light objects and micro-aneurysms of tiny dark objects. While most of the above strategies are powered by automatic analysis, they are all designed for a single-color plane or gray-scale image as a preprocessing phase. The goal of the work of Foracchia et al. was to implement a strategy for luminosity and contrast enhancement on each color plane of the RGB color space independently. This method, provided by the introduction of new colors to the image, tended to produce related artifacts that were hue-shifting. More recently, by improving the single-color plane to compensate for each channel equally and ultimately perform linear color restoration, Joshi et al. suggested a technique to prevent color artifacts. The principal component analysis (PCA) aimed to improve luminosity compensation by Andres G. Marrugo et al.

F. Binary Mask Generation

In certain instances, the black background around the field of view must not be processed, so it is important to create a binary mask. It's being used to remove the background pixels from any further analysis, and this leads to a reduction in computing time. By converging the red channel portion of the retinal image with a Gaussian low pass filter, a simplified and more robust approach for binary mask development is suggested. The images are eligible to be used as input for the DL after pre-processing the images.

IV. Knowledge Base Approaches

This section is about the different knowledge base approaches of automated DR detection. There is no specified technique that can be identified as the best and each method has its own methodologies with both pros and cons. Some may use more computer power but not much accuracy and may some have performed extremely well in training data sets but not in testing data. Following are some popular techniques that have been analyzed considering past literature.

A. Machine Learning

The telemedicine tools for mechanical exploration of outlines and knowledge tries to predict and diagnose DR using machine learning techniques, which helps healthcare professionals to share adapted treatment known as precision medicine.

The approach proposed by Revathy R. et al. was based on a Kaggle dataset of 2000 images which included 1000 images of DR and 1000 with no DR. But they have used only 122 images for each DR and no DR categories for their classification. The method was based on main 4 steps, preprocess, segmentation, feature extraction and classification into 2 categories as normal or abnormal. Number of exudates, number of micro aneurysms & hemorrhages are the two features that they have used for their binary classification. The implemented classifier was a combination of five classifiers which includes, K nearest neighbors, Random forest, and Support vector machines. As they have used more than 2 standalone ML models, the voting method was used at the end to take the average and make a single output. Below table 1 depicts different classification approaches and the accuracies they have obtained [10].

Table 1 Different classifications in Machine Learning Approach

Classifiers	Accuracy
SVM	68%
KNN	76%
Random Forest	90%
Average of all 3	82%

B. Deep Neural Network

As a part of machine learning techniques, one computer-aided medical diagnosis approach is deep learning, which requires hierarchical levels of non-linear processing stages for unmonitored learning features as well as for classifying DL patterns. The classification, segmentation, detection, recovery, and registration of the images are DL applications for medical image analysis. The figure 3 shows the difference between ML and DL.

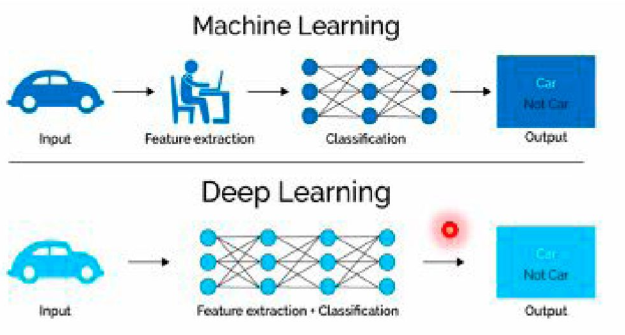

Figure 3 Difference between ML and DL approaches

Alexandr Pak et al. did a comparative study with the latest optimized approaches of DL (EfficientNet.) with two commonly used traditional architectures (DenseNet, ResNet). Based on the compounded scaling process, uniformly the distance, height, and resolution of the network is scaled, where α, β, γ are constants which can be described by grid search. In summary, Φ is an user-defined parameter that determines the amount of free model scaling resources, while the scaling dimension of a model is specified by α, β, γ. EfficientNet-b4 has been produced and used on the basis of the above principles. With different models, non-preprocessed images obtained a K (assessment value of the classification) below 0.656. The images preprocessed have a K below 0.690. The K coefficient below 0.79 is the right model we have derived by encoding network performance with the aid of ordinal regression. In relation to common models such as DenseNet and ResNet, the highest accuracy achieved on the modern EfficientNet-b4 model, which describes the sustainable advantage of EfficientNet-b4 and proper applicability in the DR detection challenge [11].

Several characteristics such as average, median, skewness, etc. will be fed as the input in the DNN methodology [12]. The hierarchical attribute learning methods came to shine with the increase in complexity and data set size, but problems such as the vanishing gradient need to be avoided. CNN and DNN performed better than conventional neural networks for this purpose. DNN models with 3-7 layers but no more than 7 layers were used in most of the studies.

C. Convolutional Neural Networks

Convolutional neural networks (CNNs) are more commonly used more than the other approaches in medical image processing, and it is highly efficient. CNN is also a feed-forward artificial neural network (ANN)[16] CNN is more likely to the ordinary neural network and also well-known deep learning architecture that neurons are organized in 2D plane to respond in the visual fields to overlapping regions. Even though the function type and sequence are usually handcrafted [15].

CNN is composed of rectangular neuron grids. Which takes as input the rectangle region of the previous layer. As well as many grids in each convolutional layer but using possibly various filters [17]. There is a pooling layer after each convolutional layer, usually in a CNN, each x_l will be a 3D array which contains length (M)× width (N) × Channels (C). Here the problem can be simplified as a binary classification problem, and we can define the loss function of the CNN as the following way.

A DL based method for DR detection, which has a feature extraction technique and a simpler decoder for a task (head), was proposed by Borys Tymchenko et al. As an initialization for the encoder, Imagenet-pretrained CNNs were used. Three decoders were used, namely the classification head that produces a one-hot encoded vector, where the each stage presence is defined as 1, the regression head that produces real numbers in the range [0,4.5), and then rounded to an integer representing the disease stage, the ordinal regression head where if the data point goes into category k, it eventually goes into all categories from 0 to 1-k. The aim of this head is to forecast all categories up to the goal. The output is produced by placing a linear regression model on three outputs of the heads. The models were combined with 3 encoder architectures for overall scoring. And the highest performance approach was 20 models (4 architectures x 5 folds) with test-time enhancements. For a pruned mean without TTA (Test Time Augmentation), ensembles scored 0.818462/0.924746 validation/test QWK (Quadratic weighted kappa) score and 0.826567/0.925466 QWK score for a pruned mean with TTA [13].

Shu-I Pao et al. proposed a bichannel CNN incorporated with the features of both the entropy images of gray level and green component for improving the accuracy, sensitivity, and specificity. Unsharp masking (UM) is used to enhance the color fundus photograph using extracted green components and used classical image enhancements tools. Green portion and the gray level of the fundus image is pre-processed by UM to increase the identification of referable DR. Then, size of 96 x 96 gray and green images generated from preprocessing stage is fed into a bichannel convolutional network that each channel with 4 convolutional layers are with 5 × 5 kernels, and the numbers of filters are 32, 64, 64, and 128 in successive layers. Maximum pooling, rectified linear unit activation function, and dropout (set to 0.3), to prevent overfitting. After flatten both layers, fully connected layers statistically determine severity of the DR This study is evaluated under accuracy, sensitivity, specificity, and the area under the receiver-operating characteristic curve (AUC of the ROC curve) and achieved 87.83%, 77.81%, and 93.88%, 0.93 respectively [14].

M. D. Abràmoff et al. has used CNN [15] and H. Jiang et al. used CNN-RestNet3 approaches for binary classification, classifying dataset into two classes only (abnormal and normal) [16]. This method shows higher performance but it does not identify the severity levels of the DR while K. Xu, et al. used CNN [17], and CNN (VGG16) was used by M. T. Esfahani et al. for multilevel classification of DR into several severity levels [18]. Table 2 and Table 3 portray a comparison between the above mentioned approaches.

Table 2 Performance comparison of Binary classification. (AUC - Area Under Curve, Acc. - Accuracy, Sens. - Sensitivity, Spec. - Specificity)

DL method	Dataset	Performance			
		AUC	Acc.	Sens.	Spec.
CNN	1000	-	94.5%	-	-
CNN-ResNet3	35000	-	85%	86%	-
CNN (Inception V3, Inception-Resnet V2 and Resnet152)	30244	0.946	88.21%	85.57%	90.85%

Table 3 Performance comparison of Multi-Level classification. (AUC - Area Under Curve, Acc. - Accuracy, Sens. - Sensitivity, Spec. - Specificity)K. Xu, M. T. Esfahani,

DL method	Dataset	Performance			
		AUC	Acc	Sens	Spec
CNN	1000	0.980	-	96.8%	87.0%
CNN (VGG16)	4105	0.848	-	89.1%	-

V. Discussion

Purpose of this paper was to critically analyze and review the existing automated methodologies of diagnosing DR using fundus images. In a wide variety of applications, for DR detection preprocessing and enhancement tasks are crucial. The easiest is the medical professional's examination of the image, where preprocessing and enhancement are needed to maintain the acquired image's consistency while trying to clarify or accentuate its structure and anatomical characteristics. In algorithmics, preprocessing and development are often used as initial steps. Analysis of images, to promote and improve the precision of anatomical features identification, recognition, and measurement. Generic image preprocessing techniques have been used in these situations, but methods should be carefully picked, and customized image preprocessing techniques should be used as per the corresponding objectives of image analysis. The benchmarking of image preprocessing tasks has been challenging and scarce due to the above-mentioned variety of uses.

Recently, the need for an effective diabetic retinopathy monitoring and diagnosis system has become a significant problem due to the growth in the number of diabetic patients. The use of DL in DR identification and classification overcomes the problem of selecting accurate ML features; it needs, on the other hand, large model training data sets. To increase the number of images and to resolve overfitting of the training process, most research has used data augmentation.

VI. Conclusion And Further Work

Researchers have applied CNNs to the collection of algorithms used for diabetic disease screening in recent years. CNNs pledge to exploit the vast numbers of images which have been obtained from raw images for clinician-interpreted screening. These models' high variance and low bias may allow CNNs to diagnose a broader variety of non- clinical-diabetic diseases as well.

Several conventional methods of classification attempt to solve the DR diagnosis problem by using image processing techniques to collect symptoms in the fundus images and implementing a classifier to make important clinical symptoms identified. The drawback of image processing techniques is that the symptom presentations are random across various types of symptoms. It is also extremely time-consuming and involves joint efforts to mark the symptom locations. Automated systems aim to learn how to make decisions directly from the image data itself, based on the modern paradigm that comes with the advent of deep learning technology. Unlike the previous methods, instead of marking symptom locations, the retinal images need to be labelled with the number of lesions. Consequently, it saves a significant amount of time during the pre-processing stage of the database [9]. To gain high accuracies well conducted pre-processing phase will be crucial.

As the further work of this study, will be a in depth analysis of the dataset and implement an automated modified DR detection method and classification system to participate in this area that is very crucial to save lives.

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