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ScienceDirect

Procedia Computer Science 132 (2018) 1432–1440

Procedia Computer Science

www.elsevier.com/locate/procedia

International Conference on Computational Intelligence and Data Science (ICCIDS 2018)

Diabetic Retinopathy: Present and Past

Ankita Gupta[a], Rita Chhikara[b]

[a] *Dept of CS/IT,The NorthCap University, Sec-23 A, Gurgaon, India*
[b] *Dept of CS/IT,The NorthCap University, Sec-23 A, Gurgaon, India*

Abstract

Diabetes, a chronic disease affects various organs of human body including the retina. Diabetic Retinopathy (DR) results from the Diabetes Mellitus (DM). In literature various machine learning algorithms have been applied in detection of DR. This involves two steps; Feature extraction and Classification. This paper reviews the various techniques used for detecting DR based on the features like blood vessels, microaneurysms, haemorrhages etc. In most of the experiments retinal fundus images were used in which images of retina were captured by fundus camera. This review bifurcates the detection of DR into two approaches; Blood vessels segmentation and Identification of lesions. This paper compares the experimental results of various machine learning techniques based on parameters like sensitivity, specificity, Area Under Curve (AUC), Accuracy. The results are also compared with the deep neural networks and analysis of best technique has been provided.

Keywords: Diabetic retinopathy, Blood vessels segmentation, Digital fundus images, Lesions

Ankita Gupta
E-mail address: ankita17csd005@ncuindia.edu

1. Introduction

DM is the main cause of blindness between a significant age group in western countries. It is increasing in under-developed countries also. Patients having DM are many more times prone to blindness than without DM. Progressive diabetic retinopathy and macular edema (clinically significant) may result in severe vision loss. It

1877-0509
10.1016/j.procs.2018.05.074

affects the retina and can even cause the blindness in diabetic patients. DR affects a large diabetic population in developed countries [32].

DR, a silent disease which comes in light only at its last stages where treatment is very difficult and in some cases impossible. It can be treated effectively only in its early stages and thus its early detection is very important through regular screening. Automatic screening is highly required so that manual effort gets reduced as expense in this procedure is quite high. To make it cost effective detection of deviations in retinal images should be automated through digital image capturing and image processing techniques. In DR blood vessels which helps in nourishing the retina starts leaking fluid and blood on retina which results in visual features known as lesions like microaneurysms, hemorrhages, hard exudates, cotton wool spots, blood vessel area [33]. Various lesions are explained as:

Microaneurysms are outpouchings of the retinal capillaries, appearing as red dots. They have increased permeability and may bleed or leak resulting in localized retinal hemorrhage or edema. Microaneurysms may occur in any condition that causes retinal microvasculopathy, Hard Exudates are well circumscribed, shiny white or cream deposits located within retina. They indicate accumulation of fluid in the retina and considered sight threatening if appear close to the macula center. They are generally seen together with microaneurysms, Hemorrhages may take various shape and sizes depending on their location within retina. Most common DR hemorrhages are dot hemorrhages. They are small round superficial hemorrhages that originate from the superficial capillary network of the retina, Cotton wool spots are yellow/white superficial retinal lesions with indistinct feathery borders. They represent areas of edema within the retinal nerve fiber layer due to focal ischemia. They usually resolve spontaneously within 3 months. If the underlying ischemic condition persists, new lesions can develop in different locations. They often occur in conjunction with retinal hemorrhages and microaneurysms and represent retinal microvasculopathy [34]. These lesions along with anatomy of retina can be shown in figure 1:

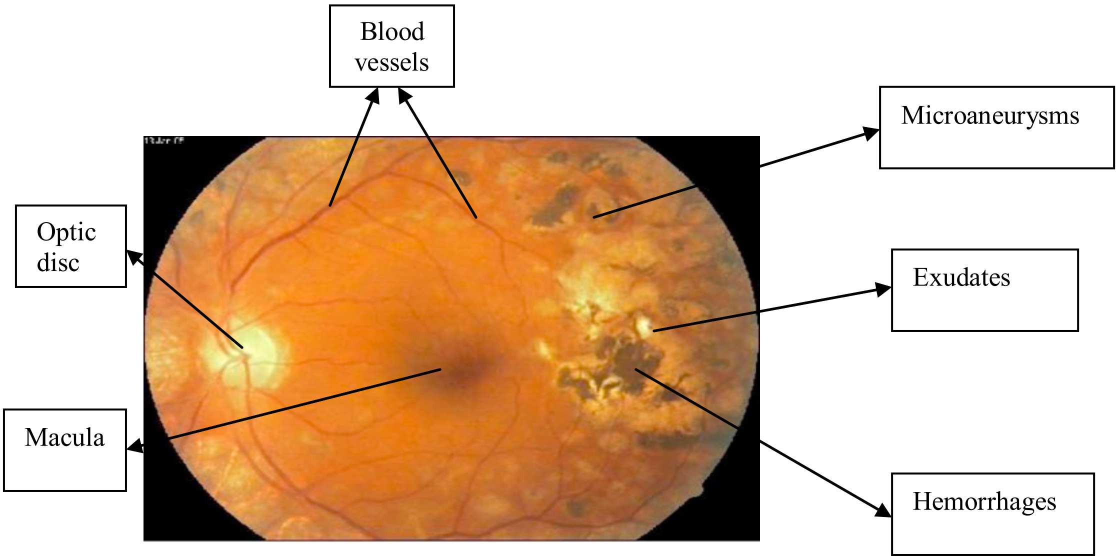

Fig 1. various lesions of retina

2. Diabetic retinopathy

2.1. Retinal fundus images

Most of the published papers [1][2][3][4] worked on fundus images as shown in fig 1 above for identifying diabetic retinopathy (DR). However fluoresceine angiography and OCT (Optic Coherence Tomography) can be used for the same. Fundus images are captured by an optical system known as fundus camera, a combination of attached camera with a low power microscope. It can be used simultaneously for both illuminating the retina along with its imaging. It has been designed for imaging the interior of the eye mainly the retina, optic disc, macula and posterior pole.

2.2. Severity of diabetic retinopathy

According to International Clinical Diabetic Retinopathy (ICDR) and Early Treatment Diabetic Retinopathy Study Research Group (ETDRS) [29] severity scale various levels of DR are defined as:

0-No apparent retinopathy

1-Mild non proliferative diabetic retinopathy- atleast one microaneurysm with or without the presence of other lesions

2-Moderate non proliferative diabetic retinopathy-numerous microaneurysms and retinal hemorrhages are present with or without cotton wool spots.

3-Severe non proliferative diabetic retinopathy –a)numerous hemorrhages and microaneurysms in 4 quadrants of the retina b)cotton wool spots in 2 or more quadrants c) Intraretinal microvascular abnormalities in atleast 1 quadrant.

4-Proliferative diabetic retinopathy-an advanced stage in which new thin and fragile blood vessels are generated having high risk of leakage and can cause severe vision loss and even blindness.

Macular Edema - exudates or apparent thickening within 1 disc diameter from the fovea- Can also result from DR which can or cannot be vision threatening.

3. Literature survey on detection of diabetic retinopathy

A lot of work has been done in this field and there are various ways for detecting DR. For its detection researchers have worked on various techniques as detecting blood vessels, various lesions such as microaneurysms, exudates, hemorrhages etc. A change in shape and size of blood vessels is a good indicator of detecting DR. In the same way presence of various lesions helps in detecting diabetic retinopathy. Thus various researches have been bifurcated in two ways as of automating blood vessels segmentation [1][5][7] and of identifying the lesions[2][3]. Thus the two most common ways are:

3.1. Segmentation of retinal blood vessels

It means to separate the blood vasculature of retina in fundus images from its background. It plays an important role not only in assessing DR which is our primary aim but also other cardiovascular and ophthalmic diseases. Also every person retina blood vasculature is different it can also be used in biometric identification. But this is a difficult task because of low contrast in fundus imaging, variable size vessels, presence of various pathologies as microaneurysms, hard exudates, hemorrhages etc. In terms of machine learning every image pixel is either a part of vessel or non-vessel decision class. Several works has been published in this area [12][15].

3.1.1. Databases used in this approach

a) DRIVE(Digital Retinal Images for Vessel Extraction)-A screening study has been conducted in Netherlands on 400 subjects of age between 25-90.This database contains 40 samples from those 400 samples in which 7 shows sign of mild DR whereas others are normal. 3ccd camera is used for each image. Both training and test sets contain 20 images taken from different patients. Manual segmentation of blood vessels is provided for every image known as truth or gold standard [14].

b) STARE (Structured Analysis of Retina)- composed of 20 retinal fundus images using TopCon TRV-50 fundus camera. This is divided into two datasets, one contain healthy subjects while the other one contains pathologies e.g. microaneurysms, hemorrhages etc. Some of these pathologies totally overlap blood vessels. Segmentation becomes more challenging when these pathologies are present [13][36].

c) CHASE- It is a database consisted of subset of retinal images taken from multiethnic children in England. It has 28 images of 1280 * 960 pixels resolution. Compared to the above two databases CHASE images are of more uniform in case of background illumination, poor contrast of vessels with background and has central vessel reflex[37].

In figure 2 the retina image along with its blood vessels segmentation for normal retina and retina having proliferative DR is depicted.

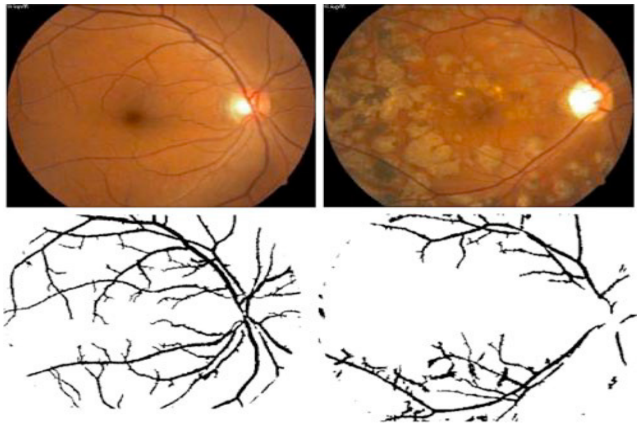

Fig 2. Normal retina and retina having DR

This paper presents a brief review of methods discussed in earlier researches for vessel segmentation along with the latest approaches.

3.1.2. Unsupervised Methods

Kande et al. [16] proposed fuzzy based segmentation by first using the red and green channels of the same images so that non-uniform illumination in fundus images can be corrected. To enhance the difference between blood vessels and background, Matched Filtering is used. In the final step vascular tree structure is found with the help of fuzzy C-Means clustering and connected component labelling. They made use of STARE and DRIVE databases. A 2D Gaussian matched filter was used by Yao and Chen [17]. The evaluation was done on the STARE database. Cinsidicsi and Aydin [18] used Ant Colony algorithm along with matched filter. They worked on DRIVE database with AUC achieved as 0.9407 and average accuracy of 0.9293. Amin and Yan [19] proposed phase congruency, a high speed method for detection of blood vessels. Fraz et al. [20] proposed a unique combination of morphological bit plane and centerlines detection of blood vessels. Various other morphological processing approaches, model based approaches, vessel tracking and multiscale approaches have been used as reviewed by [10]. Odstcilik et al. [5] proposed an approach of retinal vessel segmentation which helps in various ways as arteriolar narrowing, glaucoma and as a preprocessing step for further image analysis. For detecting diabetic retinopathy retinal vessel segmentation is important because it leads to the visualization of features like neovascular nets, hemorrhages, microaneurysms etc. For accurate segmentation of retinal vessel tree they used matched filtering (MF) along with minimum error thresholding. They have created a new high-resolution fundus image database which is publicly available as HRF. They have compared their approach on this new database with publicly available databases (DRIVE and STARE).

3.1.3. Supervised Methods

Supervised methods make use of training set which is manually processed and segmented by ophthalmologists. These predefined vascular structures are known as ground truth and they are used to guide the whole training process. Various supervised classifiers have been used for this purpose as Artificial Neural

Networks(ANN), Principal Component Analysis(PCA) for feature selection followed by ANN, K-Nearest Neighbor (K-NN) classifier[21], Gaussian mixture model[22], Support Vector Machines(SVM)[23], Multiscale Gabor filters along with PCA, Feature-based Adaboost classifier[24].

3.1.4. Deep Neural Networks

Artificial Neural Networks have already been applied widely in medical imaging, but special kind of neural networks known as Deep Networks especially CNN (Convolution Neural Networks) are producing outstanding results in automatic features extraction and classification. They have already proved themselves astonishingly great in handwritten character recognition. Deep networks [25] are very robust by using the techniques like drop out which helps the network to produce correct results even if some features are missing in the test data. Moreover ReLU (Rectified Linear Units) is used as transfer functions in deep CNNs which help in effective training as they do not vanish in extremes like sigmoid and tangent functions used with conventional ANNs. Lastly with dozens of layers in deep nets they can be easily parallelized with GPUs.

Convolutional Neural Networks(CNN) –A subclass of deep networks is a feed forward multilayer neural network trained with back propagation method which extracts the features automatically from the images and thus a rigorous feature extraction and selection step is prevented by using CNN[26][27]. It acts as a feature extraction layer and generates both low level and high level features in its different layer. For feature extraction and selection two layers are used along with a final fully connected layer for fine tuning the whole network.

Convolution layer acts as feature extraction layer which uses many different features to map with the image. For each unique feature it wants to find, it searches it in the whole image at various positions by sliding a window of that feature across the image. Thus for various features it has different feature maps. Each feature map shares the same weights and maps the same feature at different positions. With this weight sharing it has less number of weights to be learned as compared to fully connected networks.

Subsampling or pooling layer acts as feature selection which helps in reducing the spatial resolution of each distinct feature map and makes the network robust to changes in size, orientation, background of images etc. Wang et al. [4] proposed hybrid method combined of CNN and Random Forests (RFs). They performed a lot of preprocessing step to improve vessel contrast. CNN was then used to automatically extract hierarchical features which were insensitive to image scaling, translation, distortion etc. Vessel classifier was finally obtained by using RFs based on majority voting. They also made use of DRIVE and STARE databases and achieved an accuracy/AUC of 0.9767/0.9475 and 0.9813/0.9751 on the two datasets respectively.

Liskowski et al. [1] also proposed a supervised method which makes use of deep neural networks. They performed various image preprocessing techniques, though deep networks can work well on raw image data but they can work more efficiently on preprocessed images. They applied Zero phase Component Analysis (ZCA) and Global Contrast Normalization (GCN) for the same. Moreover due to small number of images in both DRIVE and STARE databases they also augmented the images with various operations as scaling, rotation and flipping, as deep networks works well on a large training set. They cross-verified their results with the help of CHASE database. Detection of each pixel as a vessel or non-vessel is done b using a m*m patch centred at that pixel. They have used m=27. A patch is made for each R, G, B channel of the image hence 3 patches are formed for a single pixel resulting a size of 3*27*27=2187. They sampled 20000 training patches for both DRIVE and STARE databases. 20 images are used in DRIVE as training set resulting in 40000 samples for example. They made use of 2 CNNs one with maxpooling and one without pooling with 3 fully connected layers in the end. The output units made use of sigmoid while hidden layer consisted of ReLU as they accelerate the learning process. Error is minimized using stochastic gradient descent. They have also made use of structured prediction in which multiple pixels are classified simultaneously by a network. Various variants of their method produced AUC>0.99 with accuracy>0.97. They produced a sensitivity>0.87 in detection of fine vessels also. Table 1 below compares the results of previous researches with the latest papers as:

Table 1: Comparison of various results

Authors	Methodology	Database	Sensitivity	Specificity	Accuracy	AUC
Lupascu et al. [24]	Adaboost	DRIVE	0.72		0.9597	0.9561
Fraz et al. [15]	Ensemble Classifiers	DRIVE/STARE	0.7406/ 0.7548	0.9807/ 0.9763	0.948/ 0.9534	0.9747/0.9768
Odstrcilik et al. [5]	Improved Matched Filtering	HRF	0.7463/ 0.7060	0.9619/ 0.9693	0.9445/ 0.9340	0.9589/0.9519
Wang et al. [4]	CNN and RF	DRIVE/STARE	0.8173/ 0.8104	0.9733/ 0.9791	0.9767/ 0.9813	0.9475/0.9751
Liskowski et al. [1]	Variants of CNN	DRIVE/STARE/ CHASE			>0.97	>0.99

3.2. Identification of various lesions

This paper reviews the techniques used in literature in identifying lesions based on manual features extraction as well as use of deep networks for their automatic extraction. Most features are extracted from Messidor database and its extension Messidor-2.

3.2.1. Databases used in this approach

Messidor and Messidor-2: Messidor dataset consists of 1200 images at 45° FOV (http://messidor.crihan.fr). Messidor-2 dataset is an extension of messidor dataset with 1748 images taken from both the eyes of 874 samples [28]. EyePACS-1: It consists of macula-centred images of 9963 subjects from May 2015 to October 2015 at EyePACS screening sites taken from different cameras [2].

3.2.2. Methodologies of lesions approach

Development of various algorithms has taken place for automated detection of these lesions [8][9]. Detecting Microaneurysms (MA) is the key for early recognizing DR and for classifying candidate regions into bright lesions and non-lesions, various preprocessing steps such as colour normalization, contrast enhancement along with fuzzy C-means clustering have been applied for image segmentation [30]. Microaneurysms have also been detected through multi-scale correlation filtering as was done in [31]. As studied above based on the various combination of these lesions DR stage is predicted. Hence most of the papers worked on distinguishing retinopathy lesions from non-lesions and then further division of these lesions into bright lesions (hard exudates and cotton wool spots) and red lesions (microaneurysms and hemorrhages).

Roychowdhury et al. [11] proposed DREAM-Diabetic Retinopathy Analysis using Machine Learning. Their approach did not reject any image for poor quality as they included image enhancement module in the initial stage. They firstly performed image segmentation so that Optic Disc (OD) and major parts of blood vasculature cannot be mistakenly considered as bright lesions and red lesions respectively. After the foreground detection they performed lesion classification in the form of hierarchy as- bright lesions and red lesions which are further classified as hard exudates and cotton wool spots for bright lesions and microaneurysms and hemorrhages for the red lesions. From 78 features for this detection they used Adaboost feature weight generation to select only 30 top features. Finally they derived the DR severity grading based on lesions combinations. They achieved 100% sensitivity, 53.16% specificity and 0.904 AUC.

Various features have been extracted from time to time along with feature selection for estimating the presence or absence of diabetic retinopathy and if present severity of DR.

Antal and Hajdu [6] proposed an ensemble based system by introducing novel screening features and ensembling of machine learning classifiers. They introduced the new concept of pre-screening of digital fundus images along with optic disc centre (ODC) and macula centre (MC) distance. For classification image quality is also assessed as a feature rather than a criterion of excluding images. They have extracted various features from publicly available Messidor dataset. Their features are also present in UCI repository. They achieved 0.989 AUC (Area Under Curve) value with two classes as 0-No retinopathy and 1-presence of retinopathy.

Abramoff et al. [9] proposed Iowa Detection Program (IDP) for detecting referable diabetic retinopathy. They worked on 1748 digital fundus coloured eye images collected from 847 people from 2005 to 2010 of France. Images were graded by 3 different retina specialists. Their IDP is a combination of previously published components and this combination was used to produce a DR index between 0 and 1 means referable diabetic retinopathy or not. The IDP produced a sensitivity of 96.8%, specificity of 59.4% along with AUC=0.937. Abramoff et al. [3] proposed an augmentation of his IDP [9] with deep learning components for diabetic retinopathy. Various previous algorithms were based on image analysis in which transformations such as mathematical morphology and wavelet transformations were used. Deep learning in which features are automatically extracted from the images itself outperforms all classical image analysis tasks. Even CNN is used in all the highest performing algorithms in the kaggle competition, which completed July 2015 [35]. They proposed that detecting DR directly by training CNN is not good but CNN can be used in lesions detection with a very high performance. They made use of Messidor-2 database which consists of 874 subjects with 1748 images, one image for each eye for each subject.

Gulshan et al. [2] proposed a deep learning algorithm for detection of referable diabetic retinopathy(RDR) which is a combination of moderate and severe NPDR and PDR and referable macular edema. They made use of EyePACS-1 and Messidor-2 publicly available databases for validation and images obtained from EyePACS in United States and 3 eye hospitals in India with a total dataset of 128175 retinal images for training. They divided their datasets into development and validation sets and they were all graded by ophthalmologists for the presence of diabetic retinopathy, macular edema and whether image quality is adequate, good or excellent. They made use of popular deep network known as CNN that learn features automatically from the pixel intensities of fundus images. A training set is given as input in which DR severity is known for each image. All the parameters for CNN were set at random and they were tuned with respect to the error produced due to the actual output and desired output. In this way CNN automatically learnt the DR severity from the pixel intensities of all the training images. CNN learns by aggregating nearby pixels to form local features and then combine these local features into global features. They made use of stochastic gradient descent for fine tuning the network. They achieved an AUC of 0.991 for EyePacs-1 and 0.990 for Messidor-2 for referable diabetic retinopathy. They established two operating points, one for high sensitivity and one for high specificity and achieved remarkable results on both databases. Table 2 below shows the various comparisons as:

Table 2. Comparison of various results

Authors	#DR classes	Method	Database	Sensitivity	Specificity	AUC
Antal et al. [6]	2	Classifier Ensemble	Messidor	0.9	0.91	0.989
Abramoff et al. [9]	2	IDP	Messidor	0.968	0.594	0.937
Roychowdhury et al. [11]	2	supervised classifiers	Messidor	1	0.5316	0.904
Abramoff et al. [3]	2	CNN	Messidor	0.968	0.87	0.98
Gulshan et al. [2]	4	Deep Learning	EyePACS-1/Messidor-2	0.975/0.961	0.934/0.939	0.991/0.990

Table 1 and 2 shows the improvement in results regarding diabetic retinopathy by current techniques which make use of deep neural networks. Hence deep networks are highly efficient for automatic selection and extraction of features in case of spatially and temporally oriented data i.e. where there is an inherent structure in data. It has improved results both in automatic detection of blood vessels segmentation as well as automatic detection of Diabetic Retinopathy (DR) from lesions as compared to the various traditional techniques.

4. Gap in Literature

As seen from the literature various machine learning techniques like Adaboost, Random forest, SVM etc. have been applied to improve the performance of detecting DR. However there is still scope of exploring more significant features which can contribute in identifying a DR image. This can be achieved by extracting more features and identifying the relevant ones through feature selection techniques. Identification of various lesions as well as blood vessels segmentation can be improved using deep networks. In recent years deep neural networks have replaced a rigorous feature extraction and selection step, though to be efficient deep networks also need a good image pre-processing as fundus images generally have a poor contrast and image quality is also highly variable. Only CNNs have been applied mostly by researchers so other deep networks can be used. Creation of a good image database for training deep networks is still in progress.

5. Conclusion

Detection of DR helps in prevention of blindness. Ophthalmologists judge the stage of DR by visualizing various features like vessels, microaneurysms etc. with the help of an ophthalmoscope. Now a day's digital imaging helps a lot in automating the process of DR. Regular screening of patients are very necessary for detection of DR stage so that they can be cured on time. This is highly required as treatment in some cases is even not possible at the later stages of DR However grading of the retinal images by ophthalmologists cost high so automated systems for the same are highly required. Various algorithms and techniques reviewed in this paper are for automating the digital screening system and for providing the results which are close to the golden truth (as set by ophthalmologists). Moreover deep networks have proved highly efficient in the detection of blood vessels as well as various lesions.

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