Automated System for Detection of Diabetic Retinopathy and Age Related Macular Degeneration in Retinal Images

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Approval

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Acknowledgment

Up and above everything, all the Glory to **ALMIGHTY ALLAH** the Beneficent, the most Merciful and Most Compassionate. It's His blessing that has given me the health and strength to do this research work.

My gratitude to my supervisor **Dr. Muhammad Moazam Fraz** for his patience, guidance, useful impact and availability throughout my research work. His guidance helped me all the way in the conducting research and writing of this thesis.

I dedicate this effort to my parents and my loving wife.

Muhammad Zubair Afzal

Abstract

Computer vision has an extraordinary reputation in medical diagnostic in the current age and it covers a wide range of diseases related to human beings, animals, and what not. The human retina is a vital part of the eye for it is responsible for the vigorous vision. People with severe diabetes tend to develop symptoms of retinal damage in the later part of their lives if they are not taken care of. Though the retinal complications instigate from insignificant signs but can cover the whole retina in the advanced stage of the disease. This research work is proposed to identify the primary sign; exudates, from the retinal images of the patients who likely to develop retinal complications or already have developed. The presented work is forecasted to work for the early diagnosis of retinal exudates that most likely appear in the impediments of diabetic retinopathy and macular degeneration. We proposed an automated system for the screening of patients that is an ensemble of image analysis as well as computer vision methods. The presented work provides the computer aided diagnosing system for the patients of diabetic retinopathy and macular degeneration. In this research, we have presented the data models and clinical practice along with the computer aided diagnosing systems. Our proposed work first regulate the uniqueness in the input images, find the potential lesions with the support of anatomical knowledge with the help of image analysis techniques. Later we used machine learning algorithms to validate the spotted lesions. Experimental results show an improved overall performance with an average accuracy of 93% and 96% for the screening of diabetic retinopathy and macular degeneration respectively. We intend to incorporate a multi-lesion diagnostic solution to stimulate the clinical practice in an effort to provide better utility.

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1

1 Introduction

Computer vision enables intelligent and efficient decision support systems for the visual data and provide tailored solutions to society. The automated screening systems in healthcare brings new dimensions in the computer vision. Augmented reality, image archiving and visuals based diagnostic systems are among very fascinating computer vision techniques that are supporting modern healthcare now a days [1]. The purpose of such an intelligent system in the healthcare is to provide support to clinicians, physicians, medical practitioners, etc. for better approaching the diagnosis [2]. A number of influenced organizations are putting a lot of resources in the field of medical imaging and diagnostic systems as they see bright future in it. Deep learning has also provided dimensions to the new area of healthcare with the inspirations from robotic surgery etc. The institutions are bringing this kind of technologies for better attracting customers and have better impact on the market. It also enables satisfaction to the customer as the outcomes can be seen visually and bring a lot of contentment for the price they pay [3].

Medical imaging has its roots to 1895 when the x-ray image was produced. Since then, there have been numerous imaging modalities around such as radiography, magnetic resonance imaging, ultrasound, electrography, tactile imaging, photo-caustic imaging, thermography, echo-cardiograph, ophthalmology, etc. Medical imaging enables anatomy of human organs and physical attribution of the organs to make it visible on a photographic plate where it can be seen what has been going inside the corresponding organ [4]. It also enables the pathologies and abnormalities to be identified when there may be. Thus it can also be supplied to the computer vision tools for the diagnostic purposes to better treat diseases. Sometimes the state and complexity of a pathology is so simple that a good decision support system with the help of computer vision tools can implement diagnostic to very good precision. In other cases, imaging modalities are brought to the clinicians to understand the topographies and decide upon those in order to set a diagnosis based on clinical learning [5].

In order to make a computer vision system intelligent enough to diagnose, detect or screen a particular pathology, deep learning takes place with training and optimizing the decision agents. One comprehensive diagnostic system has multiple fragments including feature selection, training, testing, and so on [6-9]. It usually is a result of comprehensive learning of an agent function that optimized the feature and decide upon those features that if some pathology is found in the data or not. It intakes a lot of clinical experience as well as biomedical engineering that best fits the model to incorporate a diagnostic system for a given pathology [10].

We targeted retinal modalities in our research work for finding the pathologies related to human eyes. More specifically, the pathologies that are related to the patients of diabetes in the later part of their age is focused here. Since there are multiple retinal diseases ranging from short-sightedness to retinal scars that can be so radical that it can result in total vision loss.

1.1 Diabetes and Vision Impairments

Diabetes is ever growing diseases in most part of the world which is caused by insulin deficiency and non-uniform supply of glucose to the organs in human body. It is estimated that around 30 million people were reported with type 1 diabetes in 2012 only in US. A big share, i.e. 8 million of those 30 million people were remained undiagnosed. One quarter of elder people have developed diabetes in 2012 and 1.4 million people were estimated to fell prey of diabetes every year whereas out of people aging more than 20, it is predicted that 86 million people have prediabetes condition [11, 12].

Diabetes can create disorder with the non-uniform supply of glucose to the whole body. It can severely damage one part of the body or the other. The most sever conditions arise when the diabetic patient experience poor metabolic control, pregnancy or addicted to smoking, etc. Diabetes can lead to a number of diseases such as hypoglycemia, hypertension, dyslipidemia, CVD death rates, stroke, retinopathy, kidney disease, amputations, etc. [13, 14]. A huge amount of money is spent to cure the sever conditions of such patients because it is found to be more sever where there are no resources or no means of treatment or cure of diabetes. Thus a lot of budget is required for the state to cure the patients with the sever kind of diabetes and having few other implications but not the embolic diabetes [15].

The patients with diabetes tend to develop severity of diseases with every passing day of their lives. Such diseases are related to kidney, heart, lungs and not last but least, the eye. Their vision impairment is strongly related to the stage of diabetes they are in. In the later part of their lives, they are most likely to develop retinal diseases though starting with the earliest signs. There are certain impairments that can determine the type and stage of retinal diseases such as, vascular thickening, hemorrhages, exudates, cotton wool spots, edema, swelling of the blood vessels, etc. [16].

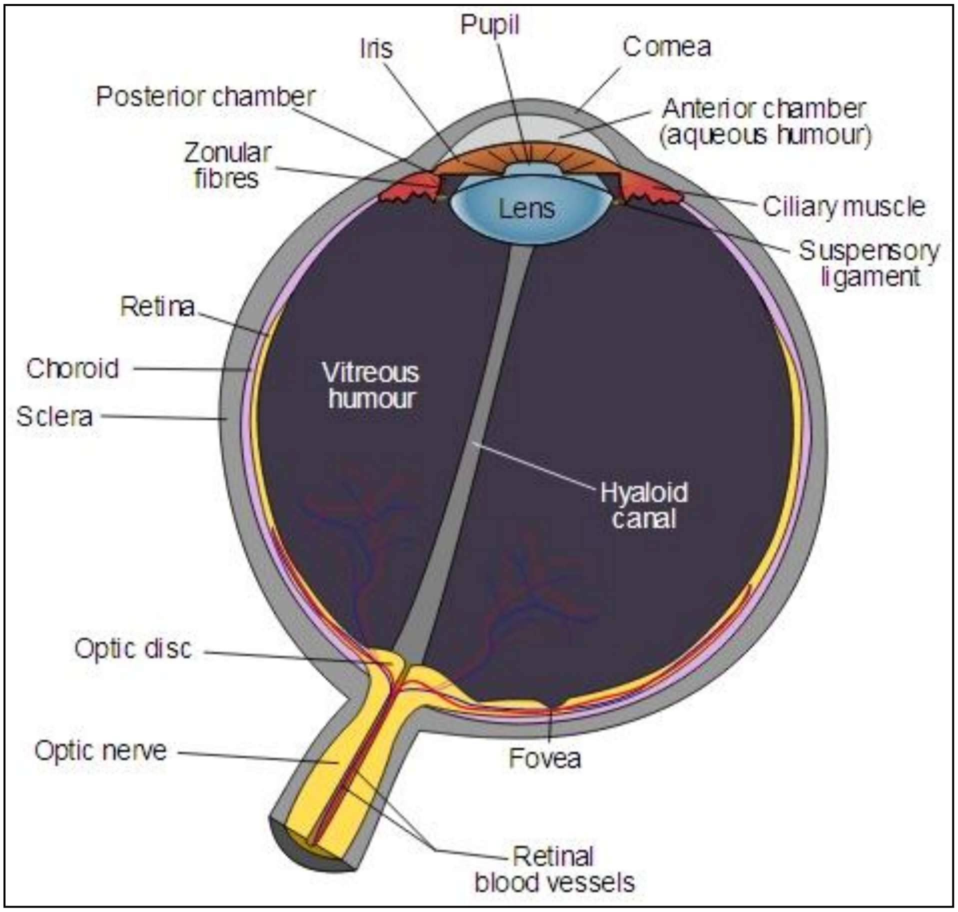

Figure 1. Anatomy of Human Eye

Retina in the human eye is vital to the vision because it is the area where a natural scene is projected and focused to be perceived by brain through optic nerve. People with diabetes over the age feel trouble focusing the scene on their retina because of non-uniform glucose supply to their blood stream in the whole body. Due to which, the glucose in the shape of fats surround the blood vessels and results in narrowing the tube to pass blood to organs [17, 18]. The pressure is absorbed by the blood vessels in retina and in result the swelling is produced on the outer side of blood vessels. In this stage, patients feel slight pain when they see bight objects, flashes or sharp scenes. In the advanced stage of diabetic retinopathy, blood vessels become weaker and develop pores on the membrane due to which fluid is leaked and seeped onto the retina [19]. In this stage of the disease, patient feel trouble when they see bright objects or illuminous scenes and also when focus to the details of the scene. The retina cannot project the scene and the details are not perceived by the brain. Instead the blurry image of the scene is projected onto the retina and sent to the brain via the optic nerve [20].

Figure 2. Vision in Mild stage of Diabetic Retinopathy

The retina becomes pigmented with different kinds of artifacts produced with the progression of the disease. It constantly keeps on producing such artifacts on all over the retina and tend to cover the central region of the retina which is called macula. In the most advanced stages of diabetic retinopathy, central region of retina becomes pigmented and the patient is highly likely to loss vision if not served with the medication or treated with swift measures. In the most advanced stages of diabetic retinopathy, patients almost cannot see the central area of the scene which mostly blacks out [21-23].

Figure 3. Vision in Proliferative stage of Diabetic Retinopathy

They need to visit the doctor frequently for their eye checkup. A most alarming situation arises when they develop diabetic retinopathy. This disease is linked to retinal deformation due to the leakage of edema from blood vessels. This situation is caused by impairments in the retinal blood streams. The manifestation of retinal diseases are determined by retinal pigmentations in different regions of retinal images. These pigmentations are discussed in the section 1.2 [2].

1.2 Retinal Pigmentation

In the beginning stages of diabetic retinopathy the conditions and pigmentations of progression is asymptotic. Later, the conditions become sever if not cured and the patient often experience blurred vision, black floater, distorted vision and vision acuity loss. Substantiated pigmentations or signs of diabetic retinopathy are given in details below.

1.2.1 Hard Exudates or Exudates

The exudates appear bright in the retinal image and are spread over the whole retina. Exudates or hard exudates are sometimes called retinal edema are caused by the leakage from blood vessels [13]. Blood vessels stream blood serum which contains serum lipids and serum proteins in retina. Resulting from diabetic retinopathy, retinal vessels become weaker because of the non-uniform glucose in the blood stream. There is an obstruction between the retinal vasculature and the retina which is called blood-retinal barrier [24]. The weak blood vessels leak blood fluid onto the retina breaking blood-retinal barrier. The deposits of the fluid onto the retina is called exudate. It can appear anywhere on the retina and the position of exudates determine the severity of diabetic retinopathy. A systematic research about the position of the exudates signifies that there are few regions that can be exudate free; such as the near about regions of optic disc, main retinal arch. Thus the absolute position of exudates are very crucial in order to find out the complexity and severity of subject [25].

Exudates are primary lesion that is considered for our research. We have regulated our research around the detection and recognition of exudates. The underlined knowledge of exudates are extensively explored and the data is also collected according to the subject. However, the other pigmentations that can also trigger the manifestation of diabetic retinopathy are discussed later.

1.2.2 Cotton-Wool Spots

Cotton Wool Spots are either seen isolated in fundus images or exist with other lesions like hemorrhages and hard exudates. Cotton Wool Spots are also seen in retina of diabetic patients but they are more closely related with hypertensive retinopathy as compared to diabetic retinopathy [26, 27]. Diabetic retinopathy is characterized by multiple hard exudates and a few CWS while multiple Cotton Wool Spots are associated with hypertensive retinopathy is one of the important characterizations of hypertensive retinopathy, and its detection is vital for early diagnosis of hypertensive retinopathy. Detection of Cotton Wool Spots is important for the building of a computer aided system that diagnoses the hypertensive retinopathy by analyzing the clinical findings that appear initially as well as at advanced stages [28, 29].

These lesions are concentrated where there is a layer of nerve fiber entering into the retina. The primary cause of this lesion is the strike or blockade in the passage of the serum fluid. Cotton-wool spots usually show high contrast with respect to the retinal background however the lesions does not grow brighter than the hard exudates. The concentrated size of lesions enable cotton-wool spots much unlikely to be distinguished as other lesions [26].

1.2.3 Micro-aneurysms

Micro-aneurysms (MAs) are among the early symptoms of DR that can be seen as round dark-red structures in digital color fundus images of retina. Early detection of micro-aneurysms facilitates timely treatment of DR and limits further complications in the retina. The variation in size, shape, intensity, and presence of other retina structures further complicate the problem of detecting MAs from fundus images [4].

Micro-aneurysms are primary pigmentation for the damaging retina causing the thinning of blood vessels. The size of micro-aneurysms can grow to 120 um. The morphology of micro-aneurysms are very less differentiable from blot hemorrhages [4].

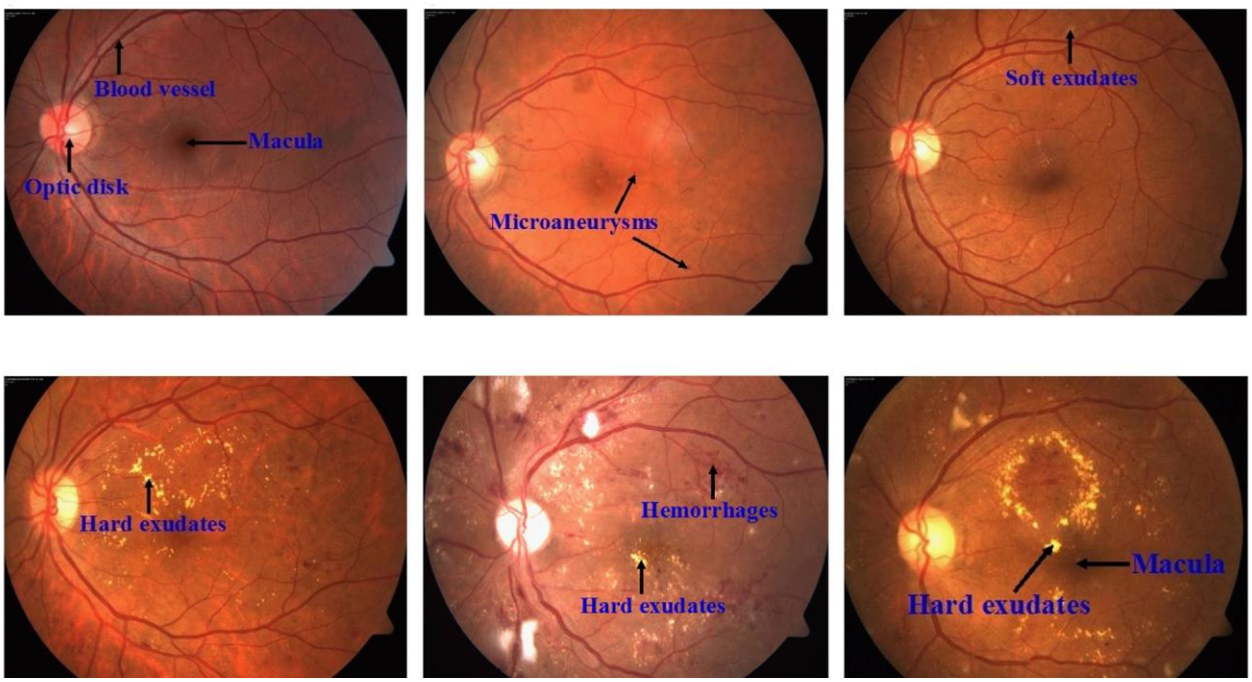

Figure 4. Vital Retinal Features and pigmentations

1.2.4 Hemorrhages

These lesions often show in the inner side of retinal layers and has the tendency of affecting different layers of retina. It is appeared as a flame or a blot in retinal image. The hemorrhages appear with asymptomatic attributes when it is manifested on the outer sides of the retina. Otherwise, it is very evident when hemorrhages are appeared close to the center of the macula [30]. The severity of disease is also triggered by the hemorrhages thus it necessitate true recognition of the lesion for the improved detection of disease. The shape is often irregular because of the spread of the fluid onto the retinal surface where it usually forms big blots with the other lesions that are causes of the progression of retinal diseases. Though these lesions are strongly attached to diabetic retinopathy, but it can also lead to the identification of malaria. The primary cause of these lesions are the leakage of blood composites form the capillaries [8].

Table 1. Significant attributes of retinal pigmentations (Clinical Knowledge)

Features	Exudates	Hemorrhages	Micro-aneurysms	Cotton Wool Spots
Location	Outside optic disc	Outside optic disc	Outside optic disc	Outside optic disc
Size	Any	Large	Small	Small
Shape	Arbitrary	Arbitrary	Round	Arbitrary
Roughness	Waxy	Dull	Dull	Fuzzy
Edges	Significant	Insignificant	Insignificant	Insignificant
Brightness	Bright	Dark	Dark	Bright
Color	Yellow	Red	Red	Yellow
Depth	Superficial	Shallow	Superficial	Superficial

1.3 Motivation

Retinal diseases have been mainstream challenge for the automated diagnostic systems that incorporate computer aided screening system for the retinal images. Multiple approaches have been practiced for the purpose and each of them has an impartial impact for which it suggests the liberty of adopting a screening system along with the medical ophthalmology. We intended to bring the distinctive approach to tailor the automated screening system by integrating image processing techniques that would be consistent irrespective of the input data. As there are numerous types of acquisition available, one such system could not address the whole sample space. Our aim is to contribute towards the assistance of the clinical ophthalmology to diagnose patients with possibility of progressing retinal diseases.

1.4 Thesis Contribution

This research work is proposed with the intentions to develop and investigate the automated diagnostic system that would be capable of detecting patients with the potential of developing diabetic retinopathy and macular degeneration. The constituents of the scheme would be ranging from the data acquisition, the image analysis techniques and the machine learning sustenance to testify the aimed examination. We experimented the proposed system on the publically available databases deliberated for the study of retinal pathologies for clinical perspectives. With the recognition of the proposed system under the cover of experimental data, we intend to serve the daily healthcare for the clinical ophthalmological practice. The research work presented here does not only provide the scheme of conducting the ophthalmological screening but to look for other dimensions where our work can be extended for procedural operations involving other rectifications.

The expansion of the presented work is to bring the mobile support with the help of handheld devices that can work for the data acquisition in mass screening. That would help in eradicating the spread and dispersion of the awareness in helping patients exterminating the causes of such a traumatic disease which could lead to complete blindness.

There are around 7 million people in Pakistan diagnosed with diabetes out of which, 3 million are above the age of 50. Those elderly diabetes patients may develop the retinal diseases such as diabetic retinopathy and macular degeneration that can lead to moderate or complete blindness. Early detection system that could assist the clinical practice to eradicate the spread of such diseases can help a great deal in ophthalmological diagnosis.

There are several considerable benefits of the proposed system that would help in ophthalmological diagnosis.

- Extraction of retinal features that are constituents of any retinal ophthalmological diagnosing system

- A robust end-to-end system that is capable of screening patients.
- Efficient utility of the clinical knowledge for the proposed subject.
- Establishment of the experimental benchmarks

The proposed methodology mainly covers the key aspects of the automated screening system in retinal ophthalmology. We have put up efforts to address these points to be able to prove our proposed methodology helpful in clinical ophthalmology.

- Retinal Feature Extraction
- Understanding the disease manifestation routines.
- Detection of diseases manifestation on account of the proposed methodology.
- Improvement in healthcare with providing assistance.
- Indexing the indicators and statistics of disease progression.

1.5 Thesis Organization

This manuscript is organized in chapters while each deliberating the purpose of introduction, implementation or the application. Chapter 1 address the whereabouts of the disease, some background knowledge of clinical practices in the field of retinal ophthalmology and the necessary utensils required to put on a well-designed screening system. The research work that has catalogued in different forms of research studies is listed in chapter 2 and the comparative analysis is also provided. The fitness and aptitude of those studies is given in terms of scientific measures used in each of the studies. Also, the scientific measures are tailored in tabular form for a better evaluation.

Chapter 3 gives the methodology adopted in our study and explains all the steps taken during the course of study. The algorithms, functions and tools are explicitly provided with the support of practical implementation. Chapter 4 deliberates the data that is used for the research. In our case, the data is extracted in the forms of datasets taken from publically available datasets. We list the characteristics of each of the datasets and provide detailed inference as input to our research work. Results under the umbrella of proposed methodology on the datasets are provided in chapter 5 with pictorial representation on real life cases of retinal pigmentation. Chapter 5 also lists the scientific measures of the algorithms used in the implementation of the proposed research.

Chapter 6 is enumerated for the discussion on the proposed research with providing the coverage of the subject. We list the accomplished milestones and draw the limitations of the proposed work as well. We also state the future endeavors and extension of the proposed work in the same chapter. Finally, the manuscript and the research drive is concluded in the chapter 7.

Chapter

2

2 Literature Review

The extensive research of recognitions systems for retinal diseases draws us the information that diabetic retinopathy falls under a few categories; majorly three. These categories are insignificantly non-proliferative diabetic retinopathy, significantly non-proliferative diabetic retinopathy and vision threatening diabetic retinopathy.

Retinal images have been used for the recognition of diseases related to the retina. We know that the retina has a stream of blood vessels where we can see other features like optic disc, arch and macula. It is very uniform area and any pigmentation appear on the retinal plate may give a lead to non-uniformity and can trigger the alarm of progressing retinal disease. A screening systems for the recognition of these features is generally a necessity for being able to provide a screening operations of these type of diseases.

The other aspect of the implementation of such a screening system is the analysis of retinal diseases in an automated way with the support of clinical practitioners. Retina has a rich package of features that can decide the healthiness of a retina and any irregularity can give lead to the identification of retinal ophthalmic diseases such as diabetic retinopathy and age related macular degeneration. We have come up with a few techniques for the detection of these features in order to be able to determine the occurrence of abnormality in the subject's retinal image. Usually it requires a huge amount of clinical experience along with the knowledge of ophthalmic diseases to obtain the process of eliminating patients with potential of developing retinal diseases.

The automated screening system is usually preferred as it reduces both time and money for the function of diagnosing the abnormalities in the long run. Philip et al. proposed an automated screening system with 99.1% positive identification rate and 97.9% negative identification rate [17]. Abramoff et al. provided a comprehensive study on the states of diabetic retinopathy and identifies that the algorithms that are available are not enough capable to replace the clinical practice of diagnosing and there are areas which needs more and more improvement [13]. Usher et al. tested an algorithm on a dataset composed of 1273 walk-in patients for the mass screening purposes with the help of a 45 degree macula centered images and yielded 94.8% identification rate which is not as good as desired in clinical practice [32]. Dupas, B. et al. emphasized the significance of automated screening system and highlighted the cause with implementing screening system with identification of retinal pigmentations with good accuracy [33]. Medhi et al. also enforced the need of a mass screening system for diabetic retinopathy as he tested his algorithm on 50 images from different databases such as Aria, DIARETDB, DRIVE, etc. and supported his claim with accuracy of 100% [34]. Since the dataset is too shallow, it does not signify the importance of the claim. Eldeeb, S.M., et al. proposed a technique for identification of macular degeneration with good accuracy but highlighted the need of improvement in developing a robust screening system [15].

2.1 Complications/Problems in DR Diagnosis

We know that the retinal tissues exposed are not very bright so that these can be captured and photographed through the illumination of itself. External source of illumination are projected onto the retina and the reflection off the pupillary plane is captured by the camera. The iris usually opens for about 2 to 8 millimeter and small size of pupil makes it even more challenging for the fundus camera [35].

There is some other complications in fundus imaging about the illumination beams that they cannot overlap to each other. In this context, separate bands are used for enlightening the pupillary plane over the distance of a few millimeters. Thus it is very obvious to the fact that fundus photography is very expensive and a lot of skill is required to operate the camera. There has been significant evolvement in the development of fundus photography for making it accessible to widen the range of functions it can be able to deliver. Film based photography has been replaced by the PACS (Picture Archiving and Communication System) in clinical ophthalmology that enables the access amongst the group of practitioners [36].

2.1.1 Image Quality

Image quality is a non-quantitative debate where we have to build some rules for a good quality of the image. For each's concern there is difference in the image quality. But here we assume that the image that depicts the best way to locate features inside is a good quality image. Such quality images are then processed to find out different abnormalities and anatomical structures in order to accomplish our research work. Image quality is hence unquantifiable but we may have some intuition of one for being invasive in details and features exposure. For a few, there could be different other parameters as number of pixels, the pixel per inch measure, size of the image, etc. but as long as we can thoroughly see different important features explicitly, we are good about working on such images [37].

2.1.2 Image Centering

Few image centering techniques are being adopted for different studies. Every fundus camera has own centering specifications where it automatically center that specified region and regenerates other structures in relation to the position of the other retinal structures.

Central region of the retina is macula which shows dark features when seen in the fundus image because of the cones present in the macula [1]. In the center of the macula is the fovea that is accountable for the finer information of the scene. The damage to the retina give lead to diabetic retinopathy rather hasty. Macular centered images are good for identifying exudates for diabetic retinopathy detection. We can avoid different contextual features of retinal images such as blood vessels, optic disc, etc. Other features are quite evident as to process to find out those features. Macular centered images are for examining patients showing symptoms of diabetic retinopathy, macular degeneration, macular edema, etc. [1, 38].

Optic disc is the part of retinal image where optic nerve enters in the eye and optic nerve head is the axons' exit point from the eye. As the nerve head region has no cones or rods so this region of the optic disc looks like a blind spot [38]. OD centered images are good in symmetry where we see different anatomical structures such as optic disc, optic nerve, optic nerve head, optic up, retinal blood vessels, etc. The fovea and macula is to either sides in such retinal images and we do not often see details specific to macular region such as exudates or micro aneurysms. These types of images are useful in locating optic disc, optic nerve head, optic cup, etc. Patients with hypertensive retinopathy, glaucoma, etc. can be identified quite easily in optic disc centered images.

2.2 Available Imaging Sources and Techniques.

For Diabetic Retinopathy, several types of Imaging has been used. Fundus photography with a specific band (red), colored fundus photography, stereo fundus photography, hyper spectral imaging, scanning laser ophthalmoscopy, adaptive optics scanning laser ophthalmoscopy, angiography with fluorescein and indocyanine and Optical Coherent Tomography (3-D OCT) are a few imaging techniques being practiced for retinal images. We have different centering techniques in imaging like fovea centered, macula centered, optic disc centered [13]. There are some magnification and angle coverage dependencies also that depends on the capabilities of the camera. Different illumination specifications also influence in this regards. Color filters are also applied in order to limit the specific band or light to study the behaviors of the image [2]. Aim of retinal photography is to get sharp images without any illumination error and reflection impairments in the photograph [2].

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We can say that the fundus images are the 2-dimensional plot of the reflected light from semi-transparent tissues present in the eye. There are few modalities or techniques that are used for fundus imaging. Those techniques are discussed here [40].

There are publically available databases for those images. These databases have images, masks, annotations, training and testing sets for experiments in the package and can be easily downloaded. A few acceptable databases are DRIVE, STARE, REVIEW, MESSIDOR, DIARETDB1, CHASE_DB1 etc. [13, 14]

2.3 Pre-Processing Techniques

Preprocessing on the images is very essential phase in order to correctly experiment on the images. It helps in reducing false positive candidates. Images that are acquired through different imaging techniques may induce blurring, reflection or illumination errors and other noise. The aim is to have a homogeneous background. For that, Medhi, J.P et al. suggested to subtract the overall mean of the image from the image for the correction of illumination [34]. Histogram equalization and then normalization is done in order to have distribution of the contrast over the entire image. Green channel of the color fundus images is suitable for preprocessing as it exhibits higher contrast between clinical features and impairments to the background of the image [41].

Priya, R. et al. proposed the extraction of green channel, histogram equalization for contrast stretching and enhancing quality and at last isotropic diffusion to remove any periodic or a-periodic noise from the fundus images [18]. Deepak, K.S et.al. extended intensity normalization and elimination of an intensity biasness for preprocessing on images [42]. Goatman, K.A et al. proposed the extraction of green channel in order to have best contrast available. Then they used grey level normalization by contrast stretching techniques. And finally the size of the image is regenerated for having similar diameter of optic disc in entire dataset [43].

Lazar, I. et al. suggested the steps for preprocessing as noise reduction, filtering and shade correction. They considered that green channel has a large of information in retinal images as it possesses higher contrast between the features and background. For noise reduction, they proposed Gaussian mask convolution and median filtering and these methods were enough beneficial that they kept the clinical features up to the mark and suppressed the noise very well [44]. Agurto, C. et al. mean shifted the image for all the channels, i.e. Red, Green and Blue to have shared mean among all the images and that they said is standard approach for histogram equalization [45]. Niemeijer, M., et al. made use of brightness correction, gamma correction and contrast enhancement for contrast normalizing [26].

Marin, D. et al. used shade correction and homogenization for better vessel segmentation [46]. Franklin, S.W. et al. used transformation from RGB to lab color space images that eradicates high correlation among those channels. Then the luminosity layer is replaced with the transformed layer and image is restored in three channels. Then mean filtering and contrast enhancement is applied [25]. J.S. et al. suggested the extraction of green channel and then morphological operations such as top-hat transform to enhance blood vessels and lesions and bottom-hat transformation to extract spots and vessels in the images [47]. Abbas, Q. et al. suggested 2 step preprocessing as CIE Lab color space transformation and contrast normalization by limited contrast adaptive histogram equalization [48].

Usman Akram, M. et al. used mean and variance based operations to separate out background to the foreground. They then removed noise by performing different intensity transformations on three channels hue, saturation and brightness [49]. Tavakoli, M., et al. stated that in order to achieve true detection of micro aneurysms, retinal images have to be preprocessed. So, they proposed preprocessing in two steps; first, to minimize the background dissimilarities and second, removal of the spots resembling micro aneurysms [50]. We now have different sources where we can get almost noise free fundus images but for better practice, we tend to induce images with a little noise so that the system can work on noisy images as well. In that scenario, preprocessing helps achieving quality of results.

2.4 Retinal Features Extraction

Beyond regular features inside human eye, there could be few irregular features that do not have support for actuality. We have patterns of different consistent features that exhibit symmetry or morphology at some particular portion or over the whole image. Those consistent features are optic disc or papilla, fovea, macula and blood vessels. In order to see the abnormalities, we often drop these consistent features and see what other features we can see in the images. Here are different comparisons need for extraction and localization of those consistent and inconsistent features.

2.4.1 Optic Disc Anatomy

Optic disc is a location in the eye where optic nerve exits the eye and is considered to be brightest part of image. Since we get eye movement when capturing retinal images, we cannot be sure of position of optic disc [51]. We have different centering techniques of imaging, i.e. macula centered and optic disc centered.

2.5 Exudate Based Screening Methods

Exudates appear yellowish with the definitive proportion and can be noticed. The presence of the exudates trigger the lead to the manifestation of retinal pathologies. Furthermore, the evidence of the exudates inside macular region signifies the progression of macular degeneration. Exudates usually form a regular shape such as cluster or Hough, appear to the outer coating of retina [10]. We provide few examples of studies that are subjected to the detection of exudates precisely from the fundus images.

Sinthanayothin et al. appends that exudates can be specifically determined by their appearance within a local neighborhood that is presenting high contrast to its neighbors

[52]. Hence they used to examine the neighboring pixels of a bright pixel on the basis of a threshold to be called a part of bright region. The method was called recursive region growing method where each pixel is recursively examined to have neighborhood within a threshold of 10. If the neighboring pixel attains intensity within threshold, it is added to the region of examination and discarded. In this way, whole image is divided into regions recursively. For avoiding variance within the region, the intensity of each pixel is replaced by median intensity of the whole region. It has to do some operations for optic disk segmentation because OD somehow appear same as exudates [52].

Usher et al. worked for bright lesion detection in retinal images following Sinthanayothin et al. [32, 52]. They preprocessed images with adaptive contrast enhancement because the contrast to the edge of images is weakening. Recursive region growing is also followed in their work along with adaptive intensity thresholding for bright regions detection. Mathematical rules are used to differentiate between lesions and noise appears in the image based on size of a region, shape, hue and intensity [32]. Sánchez et al. used histogram for probability density estimation, good statistical technique. They extracted green component of the color image and further enhanced for better segmentation of the background. Mixture model is used on the enhanced image's histogram along with dynamic thresholding. For avoiding OD in other lesion detection, OD is masked out and hard exudates are differentiated from other lesions using features such as edge strength in the enhanced green channel of image where kirsch's edge enhancement method is used [53].

Walter et al. proposed morphological based approach for detection of hard exudates. They first extracted green channel of the image. The regions that may comprise an exudate appear brighter in the image. The reason for not getting regions of high contrast in region selection is that it may contain dark vessels too. Rather they used local contrast on morphological closed image to avoid the blood vessels in the image. It generates regions where variations is thresholder and contain smaller bright regions or boundaries of larger bright regions and filling the holes would get the larger regions filled. Dilating candidate regions is used to avoid background pixels neighboring exudates. OD masking is used to avoid regions from optic disk [54].

Another morphological approach is used by Sopharak et al. for exudate detection [6]. They first transformed image into HSI for better representation of color components. Contrast enhancement is used on I band followed by median filter and then bilinear interpolation operation is used to combine neighboring pixels of smaller regions. OD is localized as high contrasted region within circular regions. Vessels are suppressed using closing operation. Local variation is used as used by Walter et al. [54] and filled using flood filling operation. The same method is used by Harangi et al. along with the information of features such as mean, standard deviation, maximum value, range, etc. [55].

Giancardo et al. used reconstruction from median filtering response of enhanced green channel rather than subtracting from the original image in preprocessing stage. Exudate candidates are selected based on 8 neighborhood analysis or stationary wavelets. Kirsch's algorithm is used to detect edges of the hard exudates [24, 56]. Niemeijer et al. used machine learning techniques for bright lesions. They processed each pixel for probability map that specifies if that pixel is part of a bright lesion. Then all pixels with high probabilities are grouped into clusters and then trained cluster features such as pixel color and cluster area are used for further probability estimation [57].

Sopharak et al. used coarse and fine exudate segmentation using fuzzy c mean clustering and morphological reconstruction respectively. They used features such as pixels' intensity, standard deviation, hue and edge pixels of the edge produced image using Sobel edge detector. Using these features, image is decomposed into clusters using Euclidean distance of the features vectors for coarse exudate detection. OD is localized by the entropy and roundness features of enhanced luminance channel of the image which is then thresholded. Fine segmentation of the rough estimation of exudates done with fuzzy c mean clustering is done using morphological dilation [58].

Fleming et al. used multiscale morphology for exudate detection. Green channel of the image is shade corrected and normalized followed by filtered for noise removal using Gaussian filter and back ground estimation is done by median filtering. OD is located using fixed perimeter circular region detection. Morphological opening is done on 5 scales and maxima of each scale is selected as threshold which further served as seed points for region growing. Region growing follows reducing threshold until the boundary of the exudates are fully contoured. They used watershed algorithm for region growing. Features used here are luminance, standard deviation, boundary gradient and area of region [17].

Sanchez et al. used local and contextual information for the inference of the candidate regions as exudates or non-exudates. They first preprocessed images with Gaussian second order derivatives of the green channels. Filter responses are used in k nearest neighbor classifier for classifying each pixel as part of candidate region. After that, local and contextual information is used to refine the candidate lesions. Local features are area of the candidate, length of the edge of the candidate, compactness of the candidate, contrast and color of candidate, mean and standard deviation of the candidate. Contextual information comprises of relationship between candidate and neighboring regions [59, 60].

Giancardo et al. used local and wavelet features for detection of exudates. Normalized image is fed for probability map where exudate candidate regions are assigned scores. After that, neighborhood component analysis is used for candidate selection. Further, exudates contours are determined by kirsch algorithm. Local features that are used for the determination of candidate regions for final selection are mean, median, standard deviation, maximum and minimum intensity values. Stationary Haar wavelet to the second stage is performed and background less image is obtained. Correlation between two form of features, local and wavelet analysis are examined for the candidate probability map [24].

2.5.1 Mathematical Morphology

Mathematic morphology arise with the basic rules from mathematical features of the image. Images are coherent with textures and these textures repeat themselves quite often. Using the details of mathematical and statistical properties of those textures, we can distinguish one part of the image to the other.

Segmentation of the exudates at finer level are described by Sopharak et al. where they used reconstruction based on mathematical morphology to detect exudates [58]. They have underwent false positives due the artifacts that are found in the retinal images such as reflection at the walls of blood vessels. They followed mathematical dilation for the morphological reconstruction by applying marker and mask of the images. Mathematical reconstruction is simultaneous dilation process resulting the fitness of a mask function on the marker function. Here marker and mask function are images which are morphed using the original mask image. They achieved accuracy of 99% with sensitivity 88.1% and specificity 99.2% [58].

Sopharak Focused on detection of exudates in backward and under developed areas and he proposed automatic detection of exudates from low contrast images without pupil enlargement. Pupil enlargement is a process where ophthalmologist use some chemical solutions to inject in the eye for capturing better and clear image which can disturb patient. He proposed methods from mathematical morphology that is efficient enough to process on low contrast images. The method proposed helped ophthalmologists to view abnormal regions highlighted and clearly visible. The performance is compared with a manual annotated design and claimed to detect features with sensitivity of 88% and specificity of 99.5% [6].

Garcia et al. Figured out that using Neural Network, hard exudates and other lesions can be detected quite easily [16]. He focused on detection of exudates for helping ophthalmologist in diagnosing development of diseases related to exudates. He used neural networks with three classifiers: Multilayer Perceptron, Radial Basis Function and Support Vector Machine. He analyzed 117 arbitrary images with variations in color and resolution. His proposed technique incurred detection of exudates from various images by normalization on the changing features of images such as brightness, contrast and color channels. He achieved sensitivity of 88.14%, 88.49% and 87.61% with Multilayer Perceptron, Radial Basis Function and Support Vector Machine respectively when analyzed on a lesion base diagnosis. However, on the image based lesion diagnosis, he achieved accuracy of 97.1%, 92.54% and 91.04% with Multilayer Perceptron, Radial Basis Function and Support Vector Machine respectively [16, 61].

Welfer et al. proposed method based on mathematical morphology for detection of exudates from fundus images. He evaluated the performance with comparison to earlier methods and claimed sensitivity of 70.84% and specificity of 98.84%. His method is extended for detection and grading of macular edema with a high accuracy of exudate detection as probable marks for macular edema. It is analyzed in the study that how exudates form circular shapes and can lead to further growth of retinal damage in other regions to [62].

Zhang et al. introduced a new database e-Ophtha_EX for the detection of exudates. They employed combination of several techniques including preprocessing, normalization, candidate regions and final exudate selection [63]. For preprocessing, they removed dark structures, bright structures and bright regions removal that correspond to the borders of retinal vessels. Different kind of contextual information is employed in order to exclude regions that do not belong to exudates regions. Using the contextual information and mathematical morphology, they extracted candidate regions. Twenty eight features were used for the final selection that came from pixel, geometry, textural and contextual based information. Random forest classifier is used for final classification of the candidate regions. They achieved 95% AUC with the new database e-Ophtha_EX at exudate level as well as image level classification. They tested the same on DIARETDB1, MESSIDOR and HEI-MED as well and achieved area under ROC curve as 95%, 93% and 94% simultaneously [63].

Youssef et al. detected blood vessels that impart detection of exudates with improvement. Non uniform illumination was removed using median filtering on the green channel along with contrast enhancement [64]. They used morphological opening which gave the bright regions only and morphological closing for leaving out the dark regions. OD is localized using circular Hough Transform and Canny edge detector for contouring the OD region. Blood vessel tree was extracted using morphological dilation followed by erosion. Elimination of blood vessel tree had given rough estimate of exudates and they used morphological reconstruction to extract final estimate of the exudates. They claimed sensitivity of 80% and specificity of 100% when experimented on STARE and NILES [64].

Harangi et al. worked for exudate detection which basically was a 3-fold scheme [35]. First they employed candidate extraction using morphological closing and reconstruction. They preprocessed the images in detail with chromaticity normalization, contrast enhancement, histogram equalization, grey world normalization, illumination correction, illumination equalization and top-hat transformation. Secondly, Boundaries of exudates were detected using ensemble of active contour method and the combination of contours to fit an energy function. Finally, regions wise classification and labeling of already contoured exudates using Naïve-Bayes classifier fed with several regions based features. They achieved accuracy of 82% on DIARETDB1 and 86% on HEI-MED databases [35].

Table 2. Morphological techniques based exudate detection studies

Algorithm	Image Dataset	Results				
		Sensitivity	**Specificity**	**Accuracy**	**AUC**	**PPV**
(Sopharak *et al.* 2010) [58]	Thammasat University Hospital Thailand	88.1%	99.2%	99%	-	-
(Sopharak *et al,* 2008) [65]	Thammasat University Hospital Thailand	80%	99.5%	-	-	-
(García *et al.* 2009a) [61]	University of Valladolid	100%	92.59%	97.01%		80.72%
(Welfer *et al.* 2010) [62]	DIARETDB1	70.48%	98.84%	-	-	21.32%
(Zhang *et al.* 2014) [63]	DiaRetDB1_v2	-	-	-	95%	-
	e-Optha_EX	-	-	-	95%	-
	Messidor	-	-	-	93%	-
	DiaRetDB1_v2	-	-	-	94%	-
(Youssef and Solouma, 2012) [64]	Institute of Laser Enhanced Sciences and STARE	80%	100%	-	-	-
(Harangi and Hajdu, 2014a) [35]	DIARETDB1	91%	68%	82%	-	-
	HEI-MED	87%	86%	86%	-	-

Table 2 compares the mathematical morphology based techniques w.r.t Sensitivity, Specificity, Accuracy, AUC and PPV. Highest sensitivity values of 96% are observed by Zhang et al. on e-Ophtha EX database [63], whereas lowest values of 70.48% are observed by Welfer et al. 2010 on DIARETDB1 dataset [62]. In respect of Specificity, 100% results are observed by Youssef and Solouma, [64] and lowest values of 86% are cited by Harangi and Hajdu [35]. Only a few results are available from Accuracy stand point, ranging from 86%

of Harangi and Hajdu [35] to 99% of Sopharak et al. [58]. Area under the Curve (AUC) and Positive Predictive Value (PPV) mostly remain un-addressed by these studies.

2.5.2 Adaptive Thresholding

Thresholding is used in image segmentation for identifying the background and foreground pixels, also known as image binarization. In adaptive thresholding, the threshold value is changed dynamically by taking into account the current pixel and its neighborhood pixel values. Thus, it is more effective when illumination gradients or background values vary significantly in a given image.

Dupas et al. Studied several approaches that are useful in detection of features for screening diabetic patients with age-related macular degeneration and diabetic retinopathy and discussed that primary feature for those diseases are retinal exudates. He proposed an algorithm based on adaptive thresholding that incur detection of primary lesions such as exudates, cotton wool spots, drusens, etc. to cause macular edema. His method achieved sensitivity of 84% and specificity of 72.7% when compared to a manual annotation against a computerized detection [33].

Abramoff et al. Emphasized on leakage of edema to from retinal exudates and the development of retinal exudates inside macula can cause retinal thickening that ultimately result in vision loss impairments. He extended that exudates can easily be segmented using adaptive thresholding on illumination channel as exudate appear bright [37].

Jaafar et al. proposed a technique based on adaptive thresholding on image regions. They first found out the homogeneity in the image and extracted all regions that are homogenous. Then they used morphological gradient for finding out the edges. They preprocessed images to exclude blood vessels and optic disc with shade correction and contrast enhancement techniques. Classification of candidate regions is done on the basis of rules. Features used in classification are aspect ratio, circularity and eccentricity. They experimented their progress on DIARETDB1 and succeeded in attaining sensitivity 99% and specificity 91%. They employed combination of DIARETDB1 and MESSIDOR databases with a group of 106 images and achieved sensitivity of 93.1%, specificity 99.2% and accuracy of 99.3% with predictive value of 78.5% [66].

Table 3. Dynamic Thresholding based exudate detection studies

Algorithm	Image Dataset	Sensitivity	Specificity	Accuracy	AUC	PPV
(Dupas *et al.* 2010) [33]	Lariboisière ophthalmology department	92.8%	-	-	-	92.4%
(Abràmoff *et al.* 2008) [37]	Unknown	84%	64%	-	84%	-
(Jaafar *et al.* 2011) [66]	DIARETDB1	99%	91%	-	-	-
	MESSIDOR	93.1%	99.2%	99.3%	-	78.5%

Table 3 compares the dynamic thresholding based techniques w.r.t Sensitivity, Specificity, Accuracy, AUC and PPV for Exudates Detection. Sensitivity results range from 84% by Dupas et al. [33] and Abràmoff et al. [37] to 99% by Jaafar et al. [66]. Lowest results of 64% are observed by Abràmoff et al. [37] and highest specificity results of 99.2% are reported by Jaafar et al. [66]. Only a single accuracy as well as PPV result has been reported by Jaafar et al. [66], which stand at 99.3% and 78.5%, respectively . AUC and PPV are mostly ignored by the dynamic thresholding based studies.

2.5.3 Machine Learning

Machine learning is of great benefit to the field of image analysis specifically for diagnosis and screening purposes. Researchers used machine learning for driving intelligence to computerized screening systems. They used supervised machine learning methods as well as unsupervised methods in order to resource maximum adaptability of the developed system. We have categorized supervised methods and unsupervised methods for providing clearer view point of individual approaches adopted by researchers.

2.5.3.1 Supervised Methods:

Schaefer et al. proposed a method for detection of exudates with the help of neural networks. His technique figured out if a certain bright region is an exudate or not based on features of that region. He thought of neural network to be capable of distinguishing exudate regions with non-exudate regions. His method achieved sensitivity of 94.78% and specificity of 94.29% [67].

Garcia et al. presented feature extraction process prior to applying machine learning and post processing for detection of exudates. They preprocessed the retinal images with normalization. For exudate detection, they first extracted few features from the regions in images where there is some probability of exudates. Logistic regression was applied to select those regions among the candidates. Finally regions those are noisy were discarded from the candidate regions after post processing [61].

Garcia et al. proposed another approach where they used classifier based on neural networks for the detection of exudates. The taken classifiers are from three different basis functions, i.e. Multilayer Perceptron, Radial Basis Function and Support Vector Machine [61]. They used image database from University of Valladolid Spain that comprises of 117 retinal images. Multilayer perceptron helped them to achieve 97% of accuracy, Radial Basis Function gave 92.5% and SVM helped them getting accuracy of 91% [16].

Giancardo et al. used features from retinal images for training of classifier in order to detect exudates. Preprocessing was done using median filtering, morphological reconstruction, background normalization and thresholding to avoid any regular or irregular contaminations. Optic disc is located using Gaussian distribution approach with knowledge of vessel thickness, orientation and concentration inside optic disc. Rough estimates of exudates were calculated using kirsch algorithm. Color analysis and wavelet decomposition were employed at pixel level for classification of exudate and non-exudate pixels. Variety of classifiers were used including KNN, SVM, Naïve Bayes and Random Forest with inference of training and testing interchangeably from different public datasets, i.e. MESSIDOR, HEI-MED and DIARETDB1. Results showed that they achieved AUC between 82% and 94% on HEI-MED, 85% to 93% on DIARETDB1 and 54% to 90% on MESSIDOR [56].

Kumar et al. implemented feature extraction based on segmentation of exudates for NPDR. Feature extraction through preprocessing involved contrast enhancement, illumination correction, morphological operations and histogram equalization and optic disc is localized by Hough transform. Two-dimensional principle component analysis was used for selecting the features that were fed to SVM for training. Classification results showed sensitivity of 97.1% and specificity of 98.3% [68].

Akram et al. proposed screening system for DME that encompasses exudate detection with respect to their position inside macular region. The system works in three phases, first is extraction of features for exudate candidate regions and making representation of those candidate regions with respect to features extracted and exact boundaries were determined using a hybrid of GMM and SVM classifiers. Macular region appears to be darker and thus GMM is used to classify amongst candidate macular regions that are represented by several features such as area, optic disc location and mean gradient magnitude. DME grading was done on the basis of exudate and respective position of them inside macular region. They evaluated their approach on two datasets MESSIDOR and HEI-MED and their results accumulated sensitivity of 98.76%, specificity of 99.02%, positive predictive value of 98.63% and accuracy of 98.72% for exudate detection [69].

Franklin et al. came up with diagnosis system for diabetic retinopathy by detecting exudates automatically. Technique discussed in their study follow candidate region segmentation, blood vessel identification and final exudate detection using several features such as color, size, texture and edge information. Contrast enhancement was done on preprocessed images for any illumination correction. Features extracted were used to train three-layer neural network and final classification is done at pixel level. They evaluated their approach on DIARETDB1 and achieved sensitivity of 96.3%, specificity of 99.8%, predictive value of 93.7% and accuracy of 99.7% [25].

2.5.3.2 Unsupervised Methods:

Pereira et al. used Ant Colony Optimization for segmentation of exudates. First they preprocessed the image with median filtering, normalization and low and high threshold. Then they used ACO that employs heuristic search and probabilistic growing. The algorithm used in their study set k ants at each iteration which tended to optimize pheromone function to establish the exudate edge localization. That formed a segmentation of the image with candidate regions and exudate were segmented out by using connected component analysis composed of 8-neighbors with a support of hard threshold. They achieved 97.5% area under ROC curve with accuracy of 97.85%, sensitivity of 80.82%, specificity of 99.16% and PPV of 73.01% when experimented on HEI-MED database [70].

Garaibeh et al. used unique approach based on probability distribution to detect exudates. Individual clusters of exudates are identified using two-fold approach, i.e. binary thresholding based on color features and edge detection based on kirsch filter. Images were preprocessed with image normalization and optic disc removal for better identification of exudate clusters. They experimented on DIARETDB0 and achieved sensitivity of 92.3%, specificity of 89.2%. Underlined principle of selecting exudate as true exudate is based on the confidence by both of sections for signifying a candidate exudate cluster a true positive [71].

Table 4. Machine Learning techniques based exudate detection studies

Algorithm	Image Dataset	Results				
		Sensitivity	**Specificity**	**Accuracy**	**AUC**	**PPV**
(Schaefer and Leung, 2007) [67]	Unknown	94.78%	94.29%	-	93.3%	-
(García *et al.* 2009b) [16]	University of Valladolid Spain	92.1%	70.4%	-	-	86.4%
(Giancardo et al. 2012a) [24]	MESSIDOR	-	-	-	90%	-
	HEI-MED	-	-	-	93%	-
	DIARETDB1	-	-	-	94%	-
(Kumar *et al.* 2012) [68]	DRIVE and STARE	97.1%	98.3%		-	-
(Akram *et al.* 2014) [69]	MESSIDOR and HEI-MED	98.76%	99.02%	98.72%	-	98.63%
(Franklin and Rajan, 2014) [25]	DIARETDB1	96.3%	99.8%	99.7%	-	93.7%
(Pereira *et al.* 2015) [70]	HEI-MED	80.82%	99.16%	97.85%	97.5%	73.01%
(Garaibeh *et al.* 2014) [71]	DIARETDB1	92.3%	89.2%	-	-	-

Table 4 summarizes the exudates detection techniques based on machine learning. We use the same comparison criteria as used for mathematical morphology and dynamic thresholding techniques. For sensitivity, the highest percentage of 98.76% have been reported by Akram et al. [69], whereas the lowest results of 80.82% have been communicated by Pereira et al. [70]. Most of the specificity results are 99% or above and the minimum specificity values stand at 89.2% by Garaibeh et al. **[71]**. Accuracy is a strong suit of machine learning techniques, with the best results of 99.7% by Franklin and Rajan, [72]. AUC and PPV have mixed results, going as low as 54% AUC by Giancardo et al. [24] and 73.01% PPV by Pereira et al. [70]. On the other end, the values for AUC and PPV reach up to 97.5% and 98.63%, as reported by Pereira et al. [70] and Akram et al. [69], respectively.

2.5.4 Model Based Approaches

The model based approaches to exudates detection use high level mathematical or probabilistic information either explicitly or implicitly. These approaches assign labels to pixels by matching them with already known object model and in certain cases; these models may include probabilities to express their uncertainty. Some of the common examples include active contour model, the Bayesian network and Kalman filter models.

Sanchez et al. proposed exudate detection using mixture models which are based on statistical features and yet are semi-parametric used for probability density estimation such as histogram. They enhanced images in the phase of preprocessing with histogram equalization. That histogram is then modeled with a mixture model in inclusion of statistical feature based dynamic threshold. That had confined bright lesions that includes exudates as well as other bright lesions. For detection of hard exudates, they used post processing that incurred edge information to decide as hard exudates usually appear with sharp edges when the image is normalized. They achieved sensitivity of 90.2% with predictive value of 96.8% and 95.2% area under ROC curve at lesion level. For image screening, they evaluated their methodology and achieved 100% sensitivity and 90% specificity [16].

Harangi et al. proposed detection of exudates with the help of model based approach based on Markov Random Field (MRF). They used morphology for preprocessing of images and then applied MRF for candidate extraction. MRF is used to minimize the energy function that helps in finding precise boundaries of exudates. That resulted in extraction of candidate regions representing true as well as false lesion because of the artifacts appearing in the image. Those candidate regions are labelled as true or false using support vector machine based upon certain features from green channel of the image such as mean, standard deviation, maximum, area of region, compactness, number of holes, etc. They experimented their technique on DIARETDB1 database and achieved 71% F-Score, 73% sensitivity and predictive value as 69% on pixel level validation. On image level they achieved 81%, 90% and 73% of F-Score, sensitivity and predictive value respectively [73].

Table 5. Model Based techniques based exudate detection studies

Algorithm	Image Dataset	Results				
		Sensitivity	Specificity	Accuracy	AUC	PPV
(Sánchez *et al.* 2009) [60]	University of Valladolid Spain	90.2%	-	-	95.2%	96.8%
(Harangi and Hajdu, 2014b) [73]	DIARETDB1	90%	-	-	-	73%

Table 5 summarizes the two research efforts, which have used model fitting techniques for the detection of exudates. Both of the works have achieved sensitivity levels of around 90%, and none of them have addressed the specificity and/or accuracy of their techniques. The AUC has only been reported at 95.2% by Sánchez et al. [60]. Our last comparison criterion, PPV has been reported at 73% and 96.8% by Harangi and Hajdu, [73] and Sánchez et al. [60], respectively.

2.5.5 Region Growing

Region growing based exudates detection techniques use the concept of seed pixels, which are chosen to initialize the segmentation process. The segmentation algorithms then repeatedly compare the pixels in the current cluster with neighboring pixels, in order to determine whether the current region could be ‘grown’ (extended) to include them as well. Commonly, a feature vector is selected for this purpose and applied to the neighboring pixels to determine their suitability.

Huiqi et al. [74] proposed region growing combined with edge detection for exudate segmentation. Their work focused on first localization of the optic disc through principle component analysis as optic disc is a largest region with bright pixels. Boundary of optic disc is categorized with active shape model with the basis of points on the outer boundary of optic disc and blood vessels inside optic disc. Noise removal was done by mean square Wiener filter on 64 sub-images and seed points in each sub-image is found by thresholding. Region growing instantiated by the seed points was done together with edge detection to find the boundaries of exudates. Sensitivity and specificity was claimed as 100% and 71% respectively [74].

Sinthanayothin et al. worked for the screening of NPDR that employed detection of hard exudates, micro-aneurysms and hemorrhages. They used region growing along with Moat Operator on preprocessed images through local and adaptive contrast enhancement. Knowledge of similar pixels within a region was used as basis for recursive region growing to detect boundaries of exudates. Sensitivity and specificity of exudate detection was recorded as 88.5% and 99.7% respectively when experimented on 30 retinal images collected from St Thomas' Hospital, London [52].

Kose et al. [75] proposed AMD screening system with an inverse segmentation method that incorporated background regions too. Instead of detecting the unhealthy regions in retinal image, their method has detected healthy regions with support of a reference feature set(s). The rest of the image regions were then classified as any of the lesions that leads to AMD. Healthy areas tend to be homogenous and they used local and adaptive regions growing methods for detection of healthy areas with seed points selected inside macular region. They used 328 images from Karadeniz Technical University and their results showed positive predictive value of 95.1%, accuracy of 98.8%, sensitivity of 98.1% and specificity of 99.8% where exudates were detected [75].

Table 6. Region growing techniques based exudate detection studies

Algorithm	Image Dataset	Results				
		Sensitivity	Specificity	Accuracy	AUC	PPV
(Huiqi and Chutatape, 2004) [74]	Different Sources	100%	71%	-	-	-
(Sinthanayothin *et al.* 2002) [52]	St Thomas' Hospital, London	88.5%	99.7%	-	-	-
(Köse *et al.* 2012) [75]	Karadeniz Technical University	98.1%	99.8%	98.8%	-	95.1%

Table 6 compares the exudate detection efforts that are based on region growing technique. Huiqi and Chutatape, [74] have achieved 100% sensitivity results, whereas the lowest sensitivity of 88.5% has been reported by Sinthanayothin et al. [52]. Huiqi and Chutatape, [74] remain on the lower end with 71% specificity values, and the highest specificity results of 99.8% have been observed by Köse et al. [75]. Only Köse et al. [75] have showcased the accuracy and PPV outcomes of their technique with 98.8% and 95.1% results, respectively. None of the other techniques have included the Accuracy, AUC or PPV in their results.

Chapter

3

3 Methodology

This chapter discusses about the methodology of research used for proposed system. It includes details and assumption of algorithms and techniques used during the course of research. Moreover, this chapter will cover different aspects of approaching to the same objective and the advantage of one approach over the other is also given. The research methodology is two-fold; one is to achieve image based screening. The other part of the research is to find the similarity of the image with severity of the disease. Dataset used for the study is listed and corresponding deliberation of the datasets is also given. This chapter will cover each and every bit of the phases of conducting research including data acquisition, pre-processing, post-processing and screening of images.

3.1 Dataset Preparation

The datasets used in our research are publically available image repositories that are comprehensively industrialized by the institutions working in the retinal ailments. We have covered a lot of literature in order to find the best sample set for our research and come up with the following repositories.

- DIARETDB0
- DIARETDB1
- HEI-DMED
- DRIVE

- MESSIDOR
- E-Ophtha-EX
- CHASE_DB1

3.2 Assumption and Notation

The main purpose of our research is to find out manifestation of diseases with the help of image processing techniques and machine learning algorithms. Our proposed system covers the automatic screening of an image that has positive matching with a diseases image. We assume that the image is characterized by the presence of exudates as positive or negative depending upon the occurrence of exudates. Furthermore, it is also assumed that the occurrence of exudates inside the macular area triggers indication of macular edema as exudates are the primary indicators for diabetic retinopathy.

About the data or an individual subject image, we assume that the image is of good quality and catered at macula. With this assumption, we assume that the optic disc would be to the either side of the macula. We take only macula centered images out of those datasets and make a database with a unique source name. We also assume that all the images incurred are RGB, i.e. with the three channels (Red, Green and Blue).

For development of our proposed system, we used MATLAB Simulink R2015a that helped us during each phase of our development. We have rigorously used functions in optimizing our objectives and sometimes we used multiple approaches each for a different aspect. We have coded in a modular fashion as to get it more familiar when re-written or submitted for consideration.

We used notations in our narration of methodologies and here are the explanation of those notations. These notations are used either in the idealization of a method or described in an algorithm. Assembling the Datasets

Since we are giving a blend of image processing and machine learning to our research. Therefore, we imply a divide of training and testing samples out of each datasets. The divide is set to be 80 by 20; i.e. the 80% of the images in one dataset is used for training and the rest of 20% is used for testing purposes. The labeling of the sample images is done manually as which image is a positive and vice versa with the help of plugged knowledge of diabetic retinopathy.

Datasets are assembled into directories which are used for batch processing or mass screening. Our proposed system would tell each image as positive or negative from one source or directory having learned the feature sets from the same source of data. The same would replicate for other sources or directories.

3.3 Detection of exudates

The first part of our proposed system is to detect the principle indicator that is exudate. The exudate commonly share some characteristics that differentiate it with other pigmentations during the retinal damage. We achieved learning of those features and screening of the images with the possible identification of those features. On the evidence of the exudates, we screen the image as positive with amplifying the impaired region to make it noticeable. The first part of our proposed system is done in a number of phases with a lot of care adopted from one phase to another. Different aspects or stages of our first phase of the research are given below.

3.3.1 Preprocessing

Preprocessing is very vital in image based augmented systems for that it provide all preceding functionalities that are cheap and quick. This process is used to obtain a generalization of the data by filtering out certain details that are important to use while discarding others. It can also reduce the size of the data which can enhance the rate of processing the data to a large proportion.

In case of images, as we know few datasets have images from very sensitive source such as MESSIDOR, it has images of a large resolutions which cannot be processed on the go. We can reduce the size of the image in the phase of preprocessing. Sometimes it can go wrong by reducing the size of the data so much that it would lose certain features that are vital for post-processing. To avoid that, we have generalization of each source of the datasets and learned that in order to preprocess all of the images symmetrically. Here we brief the pre-processing steps in the later sections.

3.3.1.1 Image normalization

Normalization of the image implies the uniformity of the image for the entire region space. It is very crucial to understand what arrangements of features appear there and what are the relationships of those features. How do they occur concurrently and how we can make them differentiable.

This section is done in the frequency domain where we normalize image frequencies with the maximum frequency occurs in the image. We apply Gaussian filtering in the frequency domain that that boosts the discrepancy in the image with exploiting the contrast between regions.

3.3.1.2 Template Matching

Template matching infers to the uniformity of the whole dataset of images that are taken from one source where the images are captured with the same equipment. There are cases where we see a few images are ignited or sometimes very deprived out of the same datasets. That gives us the lead that the taken image at the particular moment can be affected from the non-uniform illumination source and the exposure is not kept even.

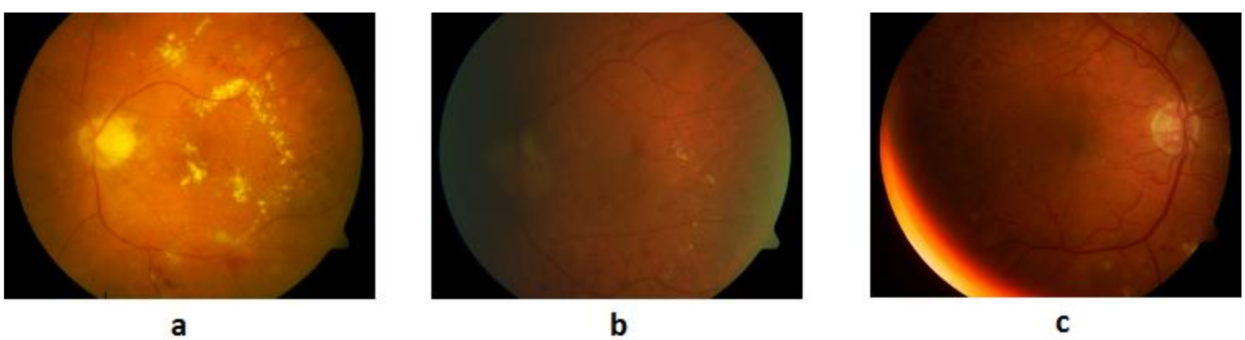


Figure 5. Images from DIARETDB0 with different exposures

Template matching is handy for transforming images to a uniform prototype of best image out of the dataset. We used a brand images out of each databases and normalize all the images according to the intensity distribution of the sample image. By performing the template matching, we come upon the datasets with uniform images having a uniform representation of the intensities.

3.3.1.3 Non-Local Mean Filtering

This technique is very suitable for removing the noise in the image. Sometimes we come up with images that have happened with a deformity in the result of some unwanted behavior during the capture. That can be a result of equipment failure or any artifacts that are produced on the equipment. There are different techniques that incur noise removal such as averaging, image smoothing etc. but that cause the whacking of significant information in the image and cannot preserve boundaries or discrepancy between regions.

Simple Averaging is an operation that performs noise reduction for us. This is typically called pre-processing of the image. It most probably retains the edges in the image but removes the empirical noise. In Median filtering, we first accumulate a filter size, 3 by 3 is smallest. We take that filter to be an odd rowed and columned because, we want each pixel to have the same number of neighboring pixels in every direction. Then for every pixel in the image, we define the filter. In averaging or filtering, we do nothing but overlap the values of the filter to the original pixels of the image.

There are some local mean filters such as the “Median” filter. For every pixel, it finds the most occurring pixel intensities in all of the neighborhoods of that pixel of interest and replaces the result with the pixel at center. The following is the procedure for a 3 by 3 filter size.

$$\mathbf{R} = \mathbf{Median}\{\, \mathbf{w(-1,-1)f(x-1,y-1)}, \mathbf{w(-1,0)f(x-1,y)}, \ldots, \mathbf{w(1,0)f(x+1,y)}, \mathbf{w(1,1)f(x+1,y+1)} \,\}$$

In the similar contest, we can perform Gaussian and other local mean filtering.

Median filtering results in a smooth image but it is sometimes important to preserve salient features such as points and edges. That can be tolerated when we perform median averaging.

Non-Local mean filtering is a concept that performs better de-noising. This is weighted averaging that takes similar type of pixels often occurring in the image. Non local mean does averaging guarantees the preservation of important features and gives the actual information expressed in the image.

Non-Local mean dictates smoothness in the image by avoiding the blurring. We cannot afford blurring effect to some important points or information in the image. As we know, when we smooth an image, we can make some edges thick or blur by averaging through a local fashion. Image may somehow be presented as smooth but when we extract edges after smoothness, we would probably come up with a thicker edge than the original one. That is worth focusing. An equation for non-local mean is as follows.

$$NL_{h,a}[u][x] = \frac{1}{C(x)} \int e^{-\frac{1}{h^2}\int R^2 G_a(t)\,[u(X+t)-u(Y+t)]^2 dt} u(y)dy$$

3.3.2 ROI segmentation

The first phase of our proposed methodology would be generation a region of interest or ROI that is significant also having marked an insignificant region of the image that can be eliminated without precaution. It would really help us eliminating a false positive response in the phase of producing resultant images after applying some filtering. As the fundus camera generates images with a specific round shape frame with a mark to distinguish the direction of the fundus head. Usually, the region of interest is very vivid as compared to the background and can be easily identified. The region of interest is differentiable with a discrete boundary that is of the fundus filter. But sometimes, due to a number of reasons, a fundus image may contain false values towards the boundary of the non-significant region of the image which needs to be discrete as show in the figure. To avoid these types of imaging malfunctioning, we define background elimination function that is very useful in further processing i.e. enhancing or normalizing the image.

Figure 6. Fundus images: (a) with discrete background. (b) with non-uniform discrepency to background

Background segmentation is done using area thresholding that is part of image morphology. The function threshold the regions of the image that has the area as specified by the given threshold. By applying prior mean filtering; given in equation 1, the image is converted to a set of more uniform regions with a shallow distinction.

$$g(x, y) = \frac{1}{mn} \sum_{(r,c)\epsilon S_{xy}} f(r, c)$$

This gives lead to have uniform regions where the intensity range of the region remains consistent throughout the region. Thus the largest connected regions with respect to area is segmented in this way. Area thresholding leaves holes between regions because of the uniformity of regions resulting from mean filtering. To avoid the holes in segmented regions, we used iterative area thresholding and hole-filling simultaneously with inducting the largest connected region consistent.

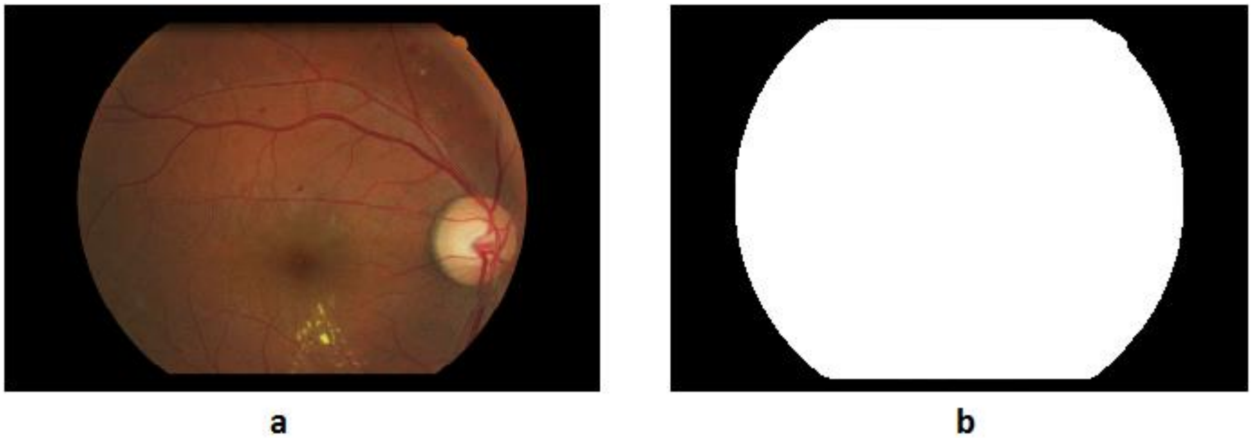


Figure 7. Fundus image (a) and ROI segmented (b)

Background elimination or ROI segmentation is useful in further processing as it gives a luxury to avoid the region where it is least probable to catch deformity.

3.3.3 Anatomical Features

As we have discussed earlier, there is a pattern in the retina that appears naturally and can be learned for modeling the feature set of the retina. The anatomic structures are given in the figure. Anatomical structures include optic disc, retinal vessels, macular region, etc. having different attributes and representation on the fundus images. For our course of research, i.e. detection of diabetic retinopathy, we need to find exudates that has discrepancy with the anatomical structures such as optic disc, vessels, etc. After a thorough research of the literature, we have established ground that in order to achieve the detection of exudates, we can eliminate a certain regions or parts of image that has negative correspondence to the likelihood of the occurrence of the exudates. We have given the details of the anatomical structures in section?. Now we explain the elimination of those structures.

3.3.3.1 Retinal vessels detection

Since the retina is packed with a network of blood capillaries and arteries commonly called vessels that are responsible of formation of exudates, it is of acute significance that we figure out where are the retinal vessels appear in the retina. As exudates only appear nearside the small vessels due to the leakage of protein fluid from those vessels, it is very obvious that exudates are highly likely to occur alongside the vessels. It gives lead to the fact that if only the exudate appear in an image, it must be near an advent of a vessel or group of vessels.

Vessels usually are of darker complexion that can best be visualized in the green channel of the image. The brightness of blood vessels on the intensity in green channel can be differentiated to that of the background areas where there are no vessels. The indication of vessels are determined by the step change of intensity. The same is true for the exudates as exudates show step change of intensity on the positive side of the intensity channel. So in order to achieve the detection of blood vessels, we need to take care of the bright regions and dark regions of the image along with the information of vessels having a step change with respect to the background to be able to detect vessels.

If we can figure out the pattern or the line width of the vessels, we can easily detect line shape features with the specified width. Since the vessels are of variable diameter ranging from large to small vessels, there is very narrow chance of getting all the vessels with the selected line width. Thresholding the intensity channel also cannot be used because there are other regions such as macula that is of darker brightness and cannot determine all of vessels.

We have done the vessels detection by the help of multi resolution analysis using wavelet transformation of the image. Wavelet transformation enables us the analysis of image on down-scaled images. Wavelet analysis is used where there are fine and coarse details in the image where the coarse level objects can be determined with down-scaled image while the fine details can be determined by the up-scaled image. It is used to capture local frequency information. The low scaled images are formed with the help of mean filtering of the image resulting a down-scaled image with the size cut to half with preserving most of the regions of the image.

We reconstruct the image from down-scaled image with interpolation that gives us the impression of uniform regions for elongated regions. After a soft thresholding, we get the regions with the area more than a threshold. Out of those regions we make a feature vector composed of bounding box area, major axis length and minor axis length. After applying thresholding on those three features, we get the areas that looks fit candidate for blood vessels. Assembling all those regions into one gives us a complete combination of blood vessels in the fundus image.

3.3.3.2 Detection of Optic Disc

The optic disc is normally brightest and largest connected region in retinal image given there is manifestation of exudates. Since exudates share similar characteristics with optic disc because of the brightness of exudates appear on the fundus image. The contextual information confronts the occurrence of exudates in the optic disc region. It is very useful to eliminate optic disc for further processing. In case of a health image, it is very easy to find optic disc with having knowledge of the optic disc being largest and brightest connected region.

But in the case of a diseased image where there are exudates present in the image it is very challenging to find the optic disc. It becomes very tricky when exudates form loopy structure and cause close resemblance to optic disc. In those cases, we need to find the location based regions that have characteristics of optic disc.

For localization of optic disc, we used adaptive histogram equalization with uniform distribution that gives us the local maximums of the regions in respective histograms. Then we form a special filter with a large log mask that exploits the regions of bright as well as dark topographies.

$$\mathbf{S} = \mathbf{Log}(\mathbf{1} + \mathbf{r})$$

We then apply that mask in the frequency domain to obtain the connected regions with either too bright or too dark attributes. After thresholding we get only the bright regions. And then we applied area thresholding using area opening with the information of the optic disc having area more than 200 pixels. We also obtain the centroids of those regions that have areas more than 200 pixels. By reconstruction the image based on those regions, we get the connected regions with the assembly of bright attributes. That simplicities the detection of optic disc with the thresholding. Having located the optic disc on the macula centered image, we also obtain the location information of the optic disc thus it becomes very apparent to say the image is of left or the right eye.

3.3.3.3 Macula detection

After having equipped with the detection of other anatomical structures such as optic disc and vessels, we have another significant region that can be associated with a high tendency of occurrence of exudates which is called macula. In case of exudates appear on the macular region, the severity of the diabetic retinopathy gives an alarming situation in the form of macular edema which is the second part of the research here.

Macula is the region where there are cones in the retina that are responsible of sharp vision and focus to the fine details with the properties of three color channel, i.e. red, green and blue. On the retinal image, it is seen dark near the center of the image if the image is macula centered. It is half of the area of the optic disc and have very gradient change in the brightness towards out of the macula. It seems like a focus to the main vascular arch when seen in the fundus image with having vertex at the optic disc forming the shape of parabola. It is of vital importance of segmenting the main vascular arch if we can correctly identifies the location of macula.

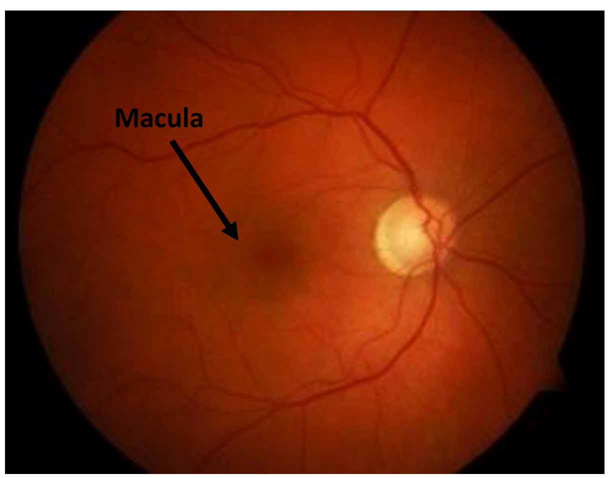


Figure 8. Macula as depicted with an annotation

The green channel of the RGB gives best annotation of macula. We extracted green channel out of the RGB image and performed histogram equalization with clip limit 0.04 and Rayleigh distribution. Then we applied median filtering 5 by 5 window size followed by thresholding using Otsu's thresholding. Out of the remaining regions, we label the regions and extract features from the regions. Those features are the bounding area, eccentricity, mean intensity, distance from optic disc centroid, entropy and arch tangent. By fitting the model of Euclidian distance between the candidate regions and a set of labelled features, we select nearest candidate and set it as the macula region. The selected macular region has the closest resemblance to the feature set we have learned.

3.3.3.4 Main Vascular Arch Detection

Through the widespread literature survey, we have established a good word that the main vascular arch has a strong discrepancy with the occurrence of exudates. Main vascular arch is the coinciding point of the blood vessels near the optic nerve head. It spreads to the either side of the retina from the center of optic disc. Since the diameter of the vessels on this region is so large that the seepage or leakage of fluid is highly vague as the bigger vessels propagate the fluid easily. Smaller vessels are tangible of dissipating the fluid onto retina making formation of exudates that are distant to main vascular arch. Having said that, we can say that the exudates are highly unlikely to appear or the main vascular arch. We have studied that main vascular arch form a parabolic shape on either side of the optic disc having the vertex right at the optic nerve head and focus towards the macular region on the positive side. That however depends on the true detection of optic nerve head and macular region. Since it gives a luxury of maintaining the regions with no risk of exudates near the main vascular arch, we can determine with a high perfection that the regions of no risk are close to the true main vascular arch.

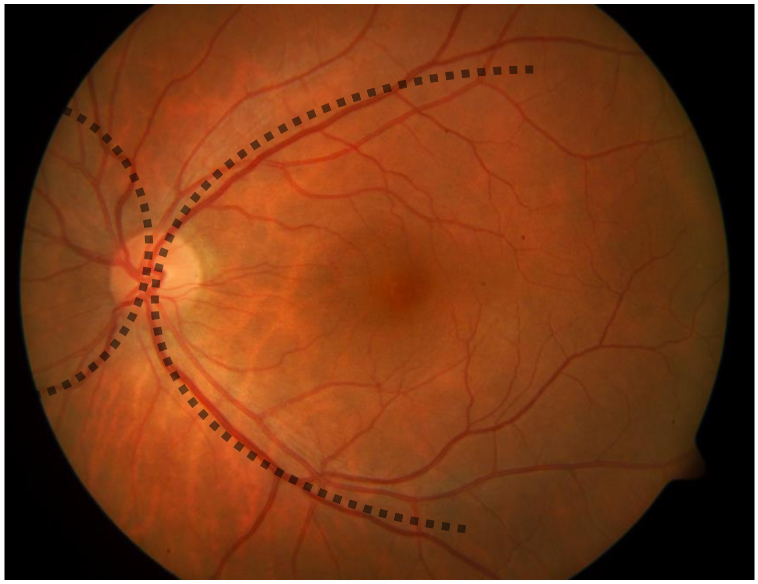


Figure 9. Main Vascular Arch as annotated by the dotted line

We have done with the detection of optic disc and macula region. We now have to fit a parabola that mostly covers the main arch by having vertex right at the localized centroid of the optic disc and focus to the one third of the distance from optic disc centroid to macula region centroid. We know that the main vascular arch appears both at the positive side as well as the negative side of the macular region. Both the arch coincide at the optic disc.

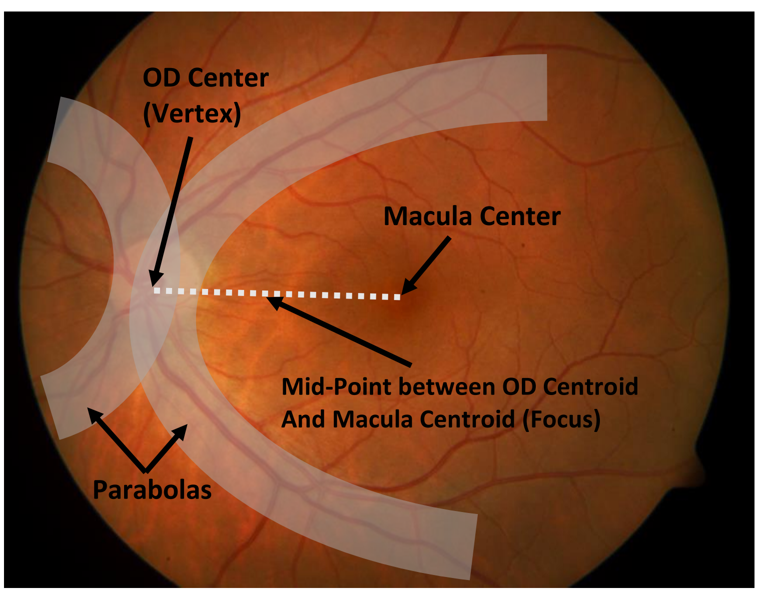


Figure 10. Elimination of the main vascular arch in the parabolic arch manner

We have let that the vertex of the parabola is at the optic disc centroid and the focus is somewhere mid-point between optic disc center and the macula center. By drawing the parabola by nominating the focus to the positive distance from the optic disc center and to the other parabola by appointing the focus to the negative distance from the OD center and Macula center.

All of the anatomical structures has a significant meaning in the course of exudate detection for screening images with the chance of diabetic retinopathy. We can take these anatomical structures into the further study where we eliminate those in a process or can segment out those regions concerning the process we are going through.

3.3.4 Candidate Exudate detection

Exudates are the primary cause of diabetic retinopathy and are a result of leakage from retinal blood vessels. In order to come up with a true exudates covering all types of images automatically is very challenging because there are a number of factors that can affect the quality of images hence proving difficult for the detection of exudates. Researchers are converging different approaches to obtain a model that can truly detect exudates out of each case and be able to establish an automated ground to practice the clinical procedures automatically that are related to ophthalmology.

Since there are a number of factors involved in the screening of patients with diabetic retinopathy, an extensive modeling is required with a huge amount of focus put to ascertain the position and composure of exudates. We provide a mix of image analysis techniques and machine learning techniques to incur the exudate detection for the purpose of screening patients with the coincidental diabetic retinopathy. We provide details of each process and also give analysis of the techniques that can also be put there. We also provide the advantage or disadvantage of techniques over each other in order to better understand what the approaches behind selecting the proposed methodology are.

3.3.4.1 Gradient filtering

We know that the exudates are of variable size and composure thus we cannot define the size thresholding to the exudate candidates. Gradient filtering of numerical vectors can tell us the occurrence of a step change as we see in the case of retinal vessels, exudates or other morphologies or pathologies occur in the fundus image. We used the variance filtering that maps the response where there are the sudden changes occur in the intensity of the green channel image.

The exudates can appear in different sizes so we can achieve the detection of exudates in two fashions; coarse level detection and acute level detection. Coarse level detection can be done using filtering or applying thresholding after mean filtering. Other methods can also come in play where we can utilize multi resolution analysis by down-scaling the image to the half of its size by applying prior averaging. But we want the detection of the exudates without losing the information of the fine or acute candidates that are also tangible for detection in the course of screening out patients with diabetic retinopathy.

Green channel is chosen because it essentially exploits the exudate regions to the background. We also know that the vessels can also be the possible response to the variance filter as vessels also exhibit a sharp boundary outwards. Competing this situation, we include two approaches, morphological closing and vessels inpainting. The morphological closing is done with the structuring element of the shape octagon because it can take down the erosion and dilation from 8 directions with a size of the structuring element equal to the diameter of the vessel of the maximum width. Then we take the supremum of the two functions to achieve the best of the image. Now the resultant image has a very smooth transition where there were blood vessels occurring and give opportunity to the exudates to bring out conspicuous. Column wise variance filtering is applied to the green channel image that is resultant from the supremum of morphological closing and vessel inpainting. We logged the response of the variance filter for the future processing.

3.3.4.2 Gabor filtering

For the granular level detection of exudates, Gabor filtering or Gabor kernel filtering has proved to be very helpful in catching the step change of the intensity with a high probability because of the log nature of the filter. Gabor kernel is produces with the scale of decomposing the intensity channel into frequency channel chosen to be 15. The circular frequency is set to be 15. We applied that filter in the frequency domain from 0 degree to 180 degree with the step of 15 degrees to catch all the step changes existing on 12 directions.

3.3.4.3 Fine level detection

The exudates can appear in very minute size that it can only be seen when pictures are enlarged to the double of the scale or sometimes even larger. One detection system would incorporate the fine level exudates with a good vintage. We have used morphological reconstruction to achieve the purpose of fine exudate detection.

In order to get a more precise shape of the candidates, an important feature for the subsequent candidate classification is used. We begin by slightly dilating the obtained rough candidates mask, using a structuring element of size 10. All pixels belonging to the resulting mask are set to zero in the original image. Then, a morphological reconstruction is applied by taking the previous image as marker and the original image as mask. Finally, the difference between the reconstructed image and the original one gives the small exudate candidates image along with the large candidates.

In order to have precise boundary, we apply a morphological top-hat with a structuring element of size of the main blood vessel diameter to the green channel of the original image. The resulting image contains the small exudate candidates. The supremum of the two response images gives the candidates contrast image. This gray level image will be extremely useful when computing candidate descriptors, as it contains precious information on their shape and contrast. Finally we perform multi-level thresholding to 10 level and by thresholding the candidate regions in the contrast image at threshold level 5. We then removed all connected components which contain less than 5 pixels (the size is fixed for all types of images because noise is almost resolution independent) we obtain the exudate candidates mask at the finer level. Each connected component of this binary image is considered in the section 3.3.4.4 as a fine level exudate candidate.

3.3.4.4 Final candidate exudate selection

The coarse level exudates and the finer level exudates are combined for the further processing. We take the assistance of supremum function that combines the two of the detected candidate images with overlapping the regions common in both of the candidate images.

3.3.5 Feature vector

Feature vector or feature matrix is used in image analysis for the inclusion of machine learning aspects to invite artificial intelligence. After the pre-processing, anatomical structure elimination and post processing, we come to the stage of applying machine learning algorithms for modelling the screening system to be efficient enough to compete the modern technologies. Machine learning is done on the basis of reasoning and probabilities. We define and deliberate an object and let the machine memorize the object and the attributes of the object. Next time we ask the machine to tell the object with the specified attributes, the machine would find all the listing of objects, compare the specified attributes with the index of the objects with listing of attributes. It matches on the basis of Euclidian distance and find maximum similarity of the attributes of an object to the given set of attributes. Once it get a finding that is closely associated to the subject attribute, it gives us result of the resultant object.

In the similar fashion, we use images as objects and the features as the attributes that define an image. We label the images into categories in our case positive or negative. And then we let the machine learn that patterns and save the information to itself.

The selection of attributes of the object is very crucial because we do not want to let the machine learn on the basis of too few attributes that it cannot thoroughly learn the patterns and come upon a learning ramble. Nor we define the attributes that are common in all the objects. Similarly we don’t want to term a large number of attributes or the attributes that are of a confusing nature. Sometimes the attributes only occur only in a few objects. Given the machine a large number of attributes cause the barrier in learning the pattern with great aptitude.

Features or attributes should be very decisive yet they should allow diversity in the domain of the procedure. We generally select the most vital features that can add up to the yield of the procedure. We keep adding the attributes to the feature set when they are contributing to the yield of the machine's recognition and notice an attribute which does not contribute much to the yield. Those attributes that do not contribute can be pruned that result in hustling of the recognition and saving us time and money.

Features selected for the course of research for selecting the true exudates out of the candidate exudates produced in the last section are given in the table 7.

Table 7. Feature Set selected for the recognition of Candidate Exudates

Features	Feature Name	Details
1	Mean of Green Channel	Mean of the green channel of the candidate exudate region
2	Maximum Intensity of Green Channel	Maximum intensity of the green channel of the candidate exudate region
3	Mean Intensity of Blue Channel	Mean of the blue channel of the candidate exudate region
4	Maximum Intensity of Blue Channel	Maximum intensity of the blue channel of the candidate exudate region
5	Major-Axis Length	Length of the orientation that majorly occupies the exudate candidate region
6	Minor-Axis Length	Length of the orientation that minutely occupies the exudate candidate region
7-14	Histogram Frequency of 8 bins of Green Channel	The tendency of occurrence of the intensities in the green channel candidate exudate region in 8bit or [0-255] intensity levels
15-22	Histogram Frequency of 8 bins of Blue Channel	The tendency of occurrence of the intensities in the blue channel candidate exudate region in 8bit or [0-255] intensity levels
23	Area	Bounding area of the candidate region
24	Eccentricity	Circularity of the candidate region
25	Compactness	Density measure of the candidate region with respect to the covered area
26	Perimeter	Number of pixels of the edge of a candidate region
27	Entropy	The unlikelihood of a candidate region to be a true exudate region

3.3.6 SVM training and testing

Next phase is to allow machine learning to come into the decision. We have a number of methods that deals with the machine learning aspects of image analysis. Supervised learning or supervised machine learning intakes a set of known data attributes and a set of outputs against those list of data attributes against one listing of data. For example, we can say height, weight, age, etc. are the data attributes and infant, kid, young, adult or old as the output against each set of the attributes against a data listing. Then we let the machine learn these attributes against the set of outputs to later recognize depending upon the occurrence of the similar attributes in any given set of data.

Suppose if we want to predict if a person has a possibility of undergoing a heart disease in this year. We have set of data attributes such as the subject's age, height, average blood pressure during a number of functions, weight, etc. and we also have the listing of people having positive or negative inclination of heart attack. The next time we face to see a subject asking about the possibility of having heart attack, we can determine by applying the modelling to the subject's attributes i.e. age, height, weight, blood pressure etc. and give a prediction of the tendency of occurrence of a heart attack in the running year.

Machine learning is categorized in two ways; supervised and unsupervised machine learning. Our course of consideration come under the supervised learning as we have a prospect of having a supervision in the form of samples that has taken already what we call the datasets. We make an agent that has the ability to decide and learn that agent with the data and corresponding attributes. This is called supervised learning as we have the data to model or train the agent prior to predict on a test set.

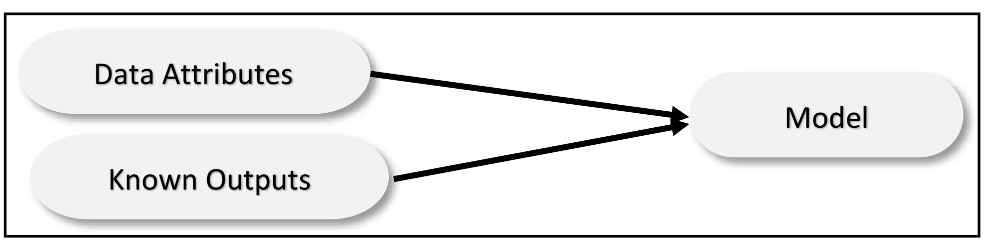


Figure 11. Supervised Learning Paradigm

Supervised learning is further divided into two categories; classification and regression. Classification is used where we have discrete number of outputs against a set of data attributes or the samples belong to a discrete number of classes such as positive or negative. In our case, the classes that define the attributes are positive and negative if there occurs any manifestations of exudates or not respectively. Regression model on the other hand is used to determine the responses that are of a target nature where it is required to achieve the performance better and better. For example, when we define attributes for a vehicle such as engine power, mileage, transmission, fuel type, etc. and the response is the number of kilometers the vehicle should cover per liter of fuel. Here the response could be any number corresponding to the given attributes. So we cannot classify or group the data since there are many responses in the sample space.

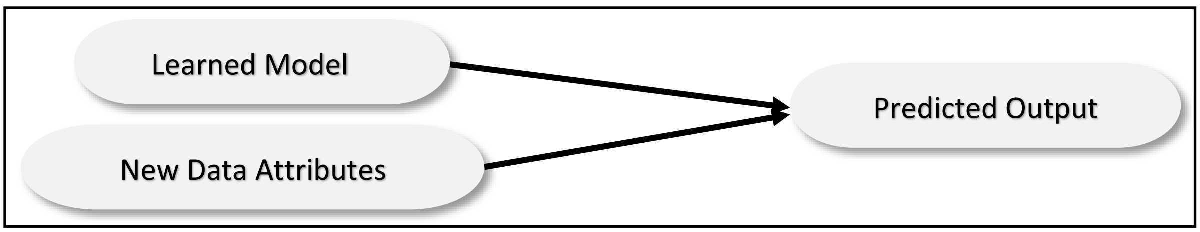


Figure 12. Prediction paradigm of Supervised Learning

The steps involved in the supervised learning include preparation of data, choosing an algorithm, learning of a model, choosing a validation style, optimizing the model and prediction on learned model. We elaborate each one of the steps according to the course of execution.

3.3.6.1 Preparation of Data:

The datasets are organized with respect to the availability of lesions, i.e. exudates in the retinal images. Datasets are labelled with positive and negative in case of the availability of exudates in individual image. An index with numeric vector is maintained in order to quantify on scientific measure.

3.3.6.2 Learning Algorithm:

As the data is linearly separable, we need a binary classification algorithm which is efficient in time, space, accuracy, transparency and interpretability. For linearly separable data, SVM seems best fit under the specified attributes. It boosts learning and provides better memory efficiency and interpretability. We used support vector machine for a binary classification model that support function optimization using objective-function minimization.

3.3.6.3 Choosing a Validate Style

We used "fitcsvm" provided by MATLAB for that it can cross validate the SVM model. It provides a support vector machine model that is trained under the provided learning data and labels from the index we have composed in the first step. The other methods are specialized for either multiclass analysis or regression.

3.3.6.4 Fitting a Model

Fitting a model function includes learning of the agent under the chosen algorithm with validation method using the provided learning data along with the labels corresponding to the learning data.

3.3.6.5 Optimizing the learned model

Optimizing the model means intensifying the efficiency of the algorithm using the appropriate method. Optimizing can result in increased performance, quick learning and classifying and better prediction. We used "compact" for SVM method that prunes the data attributes that is unnecessary or least necessary for the classification.

3.3.6.6 Prediction Method using Optimized Model

We have now optimized a model, chosen the validation and ready for the prediction. Prediction is performed with "predict" method provided by MATLAB to which a test data and a fitted model is supplied. It provides the predicted response with referencing to the learning index.

3.4 Detection of Macular Degeneration

Macular degeneration describes the deformities manifested in the macular region. It is most sever stage of diabetic retinopathy and requires immediate care. To the best of our knowledge and prolonged review of the literature, there has been no dataset that is subjected to macular degeneration only. The proposed work would enlighten the establishment of datasets, manually labeling the region of interest of macula and maintaining an index with numeric vector. The second part of the research work is to match similarity of the macular ROI to the first part of the research. The same processes are replicated for the detection of macular degeneration.

3.4.1 ROI of Macular Region

For taking off the second part of the proposed research work, we need to bring knowledge of the macular region that is manually annotated during the phase of dataset preparation as we did during the first stage of research. The macular region is near the center of the macula centered image and has a set of disperse attributes. We tend to find the exudates inside the macula region for the manifestation of macular degeneration.

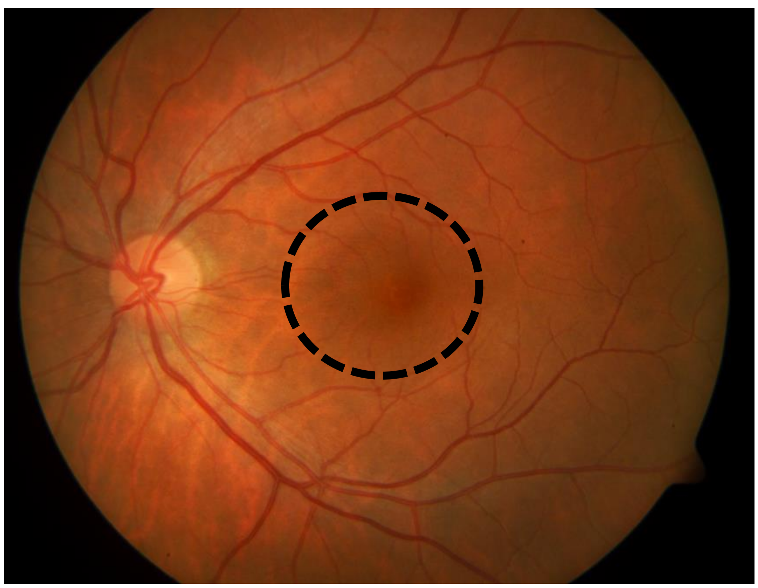


Figure 13. Macular Region annotated with a circle

Using the clinical knowledge, we maintained the datasets and annotated the region manually. We have indexed the datasets with positive and negative vector according to the availability of exudates inside the macular region.

3.4.2 Detection of exudates inside Macula

The same method that was used in the detection of exudates is invoked with changing the ROI; changing the region of interest to be the macula only rather than the whole retina. We have detected the exudates in the retinal images and we found out the similarity between the predicted responses with the macular ROI.

The macula is not congruent throughout the dataset but it can change its demonstration from case to case. The macula of an elder person will not be the same of a young patient. Though the macula detection is done in the detection of exudates (first phase of the research) but here it is necessary to stretch that the manual labeling of the macula does require the clinical knowledge. The macula does not certify the boundary or edge enclosing the macular region but it fades away spreading outward. So a deep knowledge of retinal pathologies would come in big time in this aspect.

For the sake of conduction of the proposed work, we have gotten a slight of the clinical knowledge and based on that, we marked the regions under the label of macula that is to the center of macula centered images. Thus maintaining our own dataset for the classification and analysis of the most sever type of diabetic retinopathy, i.e. macular degeneration extracted from publically available datasets. There has not a single dataset marked for the macular degeneration to the best of our knowledge and we are keen to preserve it for the further analysis and future endeavors.

Chapter

4

4 Materials

Materials for the underlined research work are the listings of images from different sources we call datasets. Each of which is organized by either a research or a clinical institution for the purpose of obtaining the artificial intelligence in diagnosing retina related diseases. Those image datasets serve number of purposes including diagnostic support, research collaboration and repository construction. Publically available datasets are organized by the virtuous institutions. Valued resources are utilized in the construction of a dataset. The first phase of which is the capturing of images with a suitable equipment under a controlled environment where the patients can also take part. Next is to collaboration with the image processing tools to maintain the quality of the image. Further, the clinical experts come into play where they hypothetically analyze each image and stimulate the ramifications in the case of occurrence. That requires a deep knowledge though and commitment to take each individual image and annotate the subjected area or region with thorough lookup. For the machine learning repository construction, an index with the reference values to the pixel and a number of collective features expressing the deformities are also required.

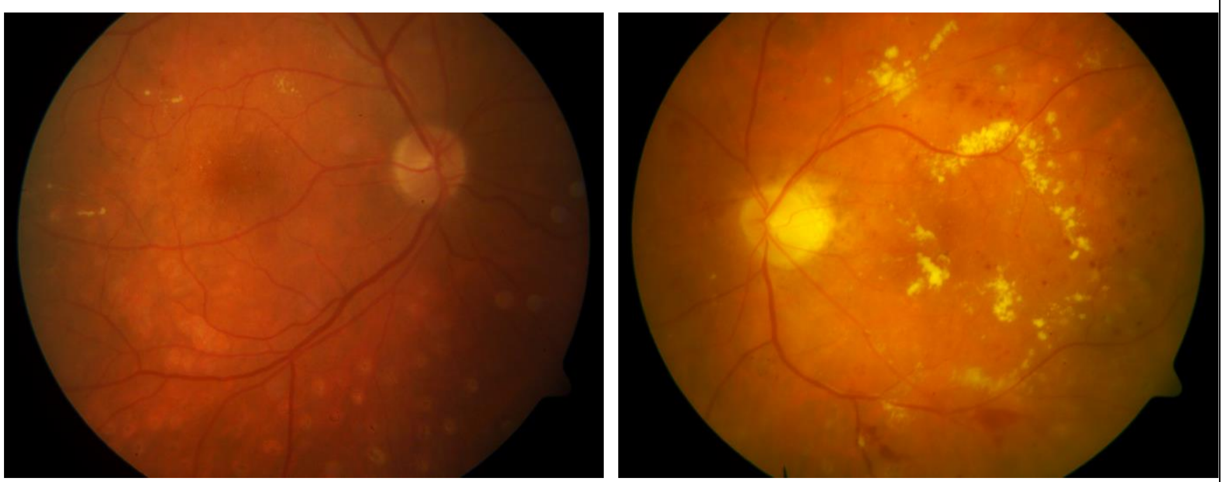
A few of the publically available datasets on retinal images serve our purpose of research. We list each of them with the degree of knowledge provided along with those images. We also present a competitive analysis of the datasets that convey the coverage of the subject from each of the datasets.

4.1 DIARETDB0

It is maintained by the university in Finland named Lappeenranta University of Technology and specifically by the Laboratory of Information Processing. The group worked for this research attempt named “ImageRet” was Machine Vision and Pattern Recognition Research Group of the above mentioned institute. It is free and available on demand when you request the source administration .

This dataset is solely made up for the detection of diabetic retinopathy and for the collaboration of research in diagnostic study related to retinal diseases. Same dataset can be used to detect different other diseases related to the retina than diabetic retinopathy. Those diseases include glaucoma, hypertensive retinopathy, maculopathy, etc. The images in this database are acquired from digital fundus camera with 50 degree FOV though other settings of the camera like aperture, focal length, illumination source, etc.

The images from this datasets are vibrant and with varying attributes that provide diversity and solid base for a disperse diagnostic purpose. It contains images with different view field, different illumination and different kind of cases ranging from normal to vision threatening. A few from the database is listed here to get the idea of the diversity of the images that are under study .



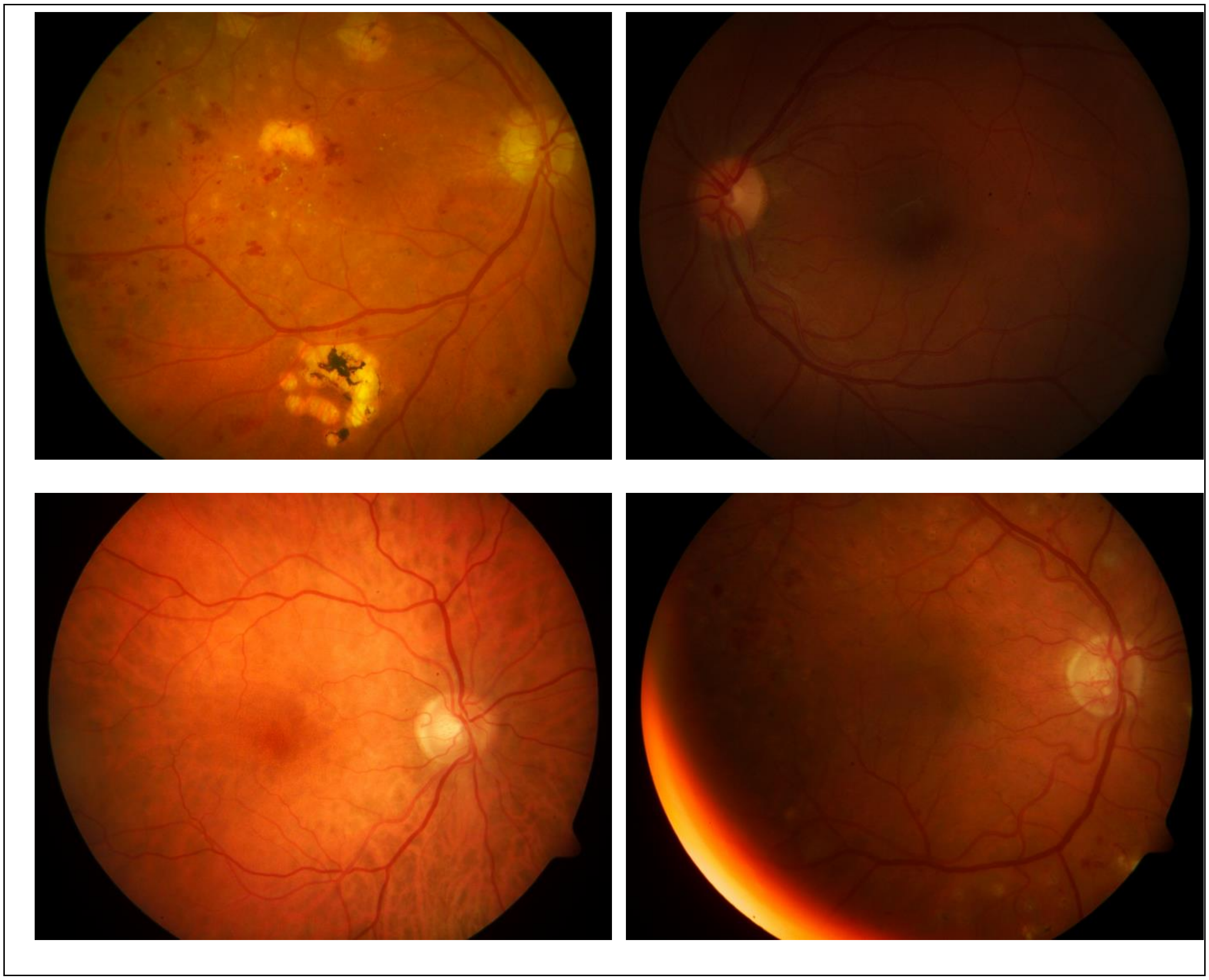


Figure 14. Sample Images from DIARETDB0

4.2 DIARETDB1

This is the second version of the same endeavor done in the DIARETDB0 by the same group of researchers. It is for the collaboration of the researchers in the field of machine learning to automate the diagnostic of diabetic retinopathy. The only noticeable difference here is the annotation and manual marking of the deformities by four medical experts. It contains 89 images acquired with a digital fundus camera with 50 degree of FOV. The images are of varying camera settings, aperture, focal length and illumination .

The ground truths, unlike the earlier version of "ImageRet" is marked with four annotations with the measure of collective confidence by the medical experts. The depiction of the ground truth established is given here.

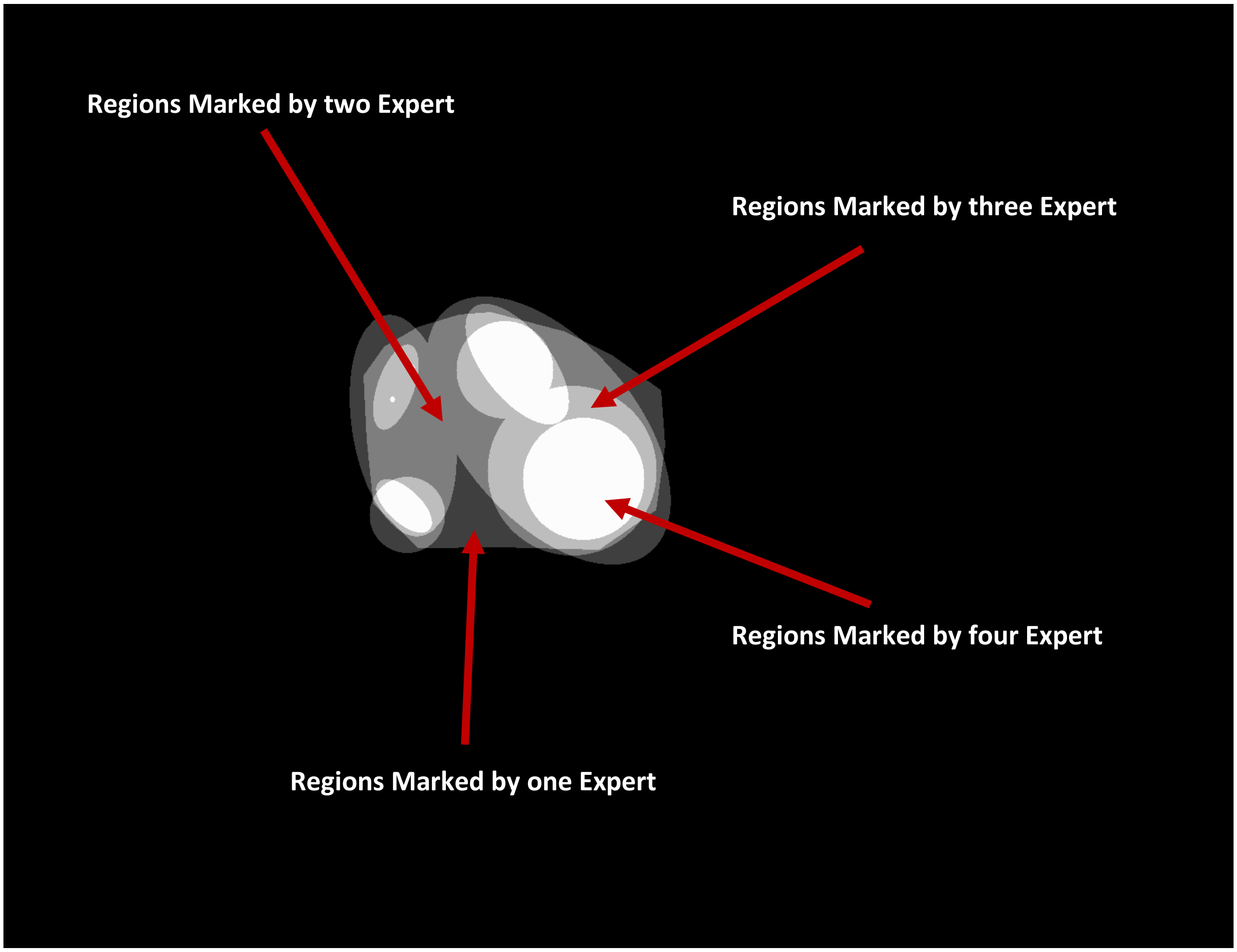


Figure 15. Annotation of Hard Exudates in DIARETDB1 from four medical experts (brighter color depicts the mutual confidence of the experts)

We take out the confidence of less than four to be absolutely sure that the region specified is actually belonging to the exudate region. The brightest elements in the ground truth refer to the exudates annotated or marked by all four medical experts. We eliminate any margin of error by just taking the regions with quadruple measure of confidence. The resultant ground truth looks like figure 16.

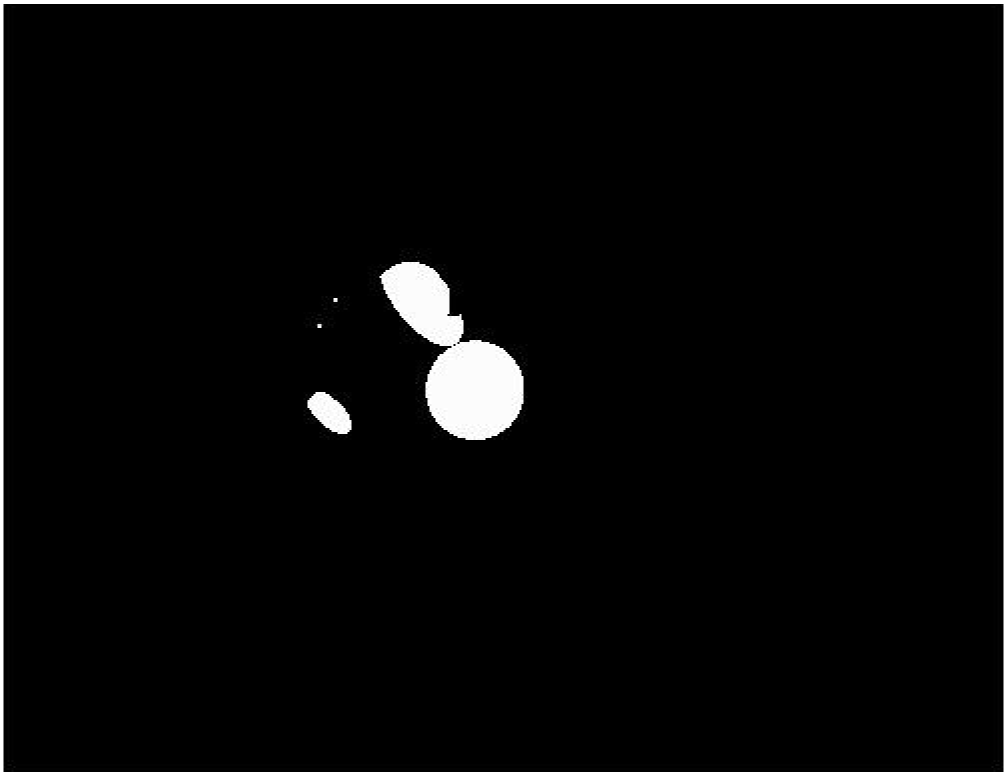


Figure 16. Ground Truth from DIARETDB1 with confidence from four medical experts

The toolkit for the provisioned annotations is also provided with the database and a feature matrix of the datasets for training and testing. Manuals for the blood vessels is separately provided for diagnosing diabetic retinopathy from other proportions. The database wholly consisted of 45 images, ground truths and vessel bank responses. The potential remunerations of the database is provided in the table 8.

4.3 HEI-MED

The dataset is organized by the group working for diagnostic of diabetic macular edema. The group was titled as Machine Vision Group at the ORNL that was established at the University of Bourgogne, France. The dataset was composed of the images taken from Hamilton Eye Institute. Hamilton Eye Institute is a primary part of the University of Tennessee of Health Science Center at Memphis, TN, USA. HEI-MED is named after the group worked for the diagnostic of diabetic macular edema and named the dataset as the Hamilton Eye Institute Macular Edema Dataset .

The group worked for the detection of diabetic macular edema that is subjected to have premier detection of exudates and the macular center. They claimed 98.8% true detection of macula in 169 of the images in HEI-MED .

4.4 MESSIDOR

Messidor is a massive datasets supports the retinal diseases diagnosis on a vast scale. It covers the subject very well and have a huge support to cater the digital fundus photographs to be monitored in an automated way. A number of researchers have gone through the dataset in the implementation and application of automated retinal diseases. Those researchers have taken advantage from the dataset as it provides different algorithms as well as the primitive indexing methods for the scientific measure of the algorithms .

The project worked for this dataset was TECHNO-VISION program that was funded by the French Ministry of Research and Defense back in 2004. The main objective of this dataset is to enable the computer assisted diagnosis of the retinal diseases such as diabetic retinopathy. It keeps the support of the research community so that the test results and algorithm performance measures are invited for the competitive analysis. It has support of archiving the algorithms, the outcome results and the performance measures of those algorithms that were researcher on the subject of diabetic retinopathy. The annotation was separately provided for the support of ground truth competence and comparison. The whole framework is supported by the internet protocol to centralize the scheme for competitive analysis. All the researchers contributed to this repository maintained the stage of archiving the details of the algorithm and performance measure through the infrastructure.

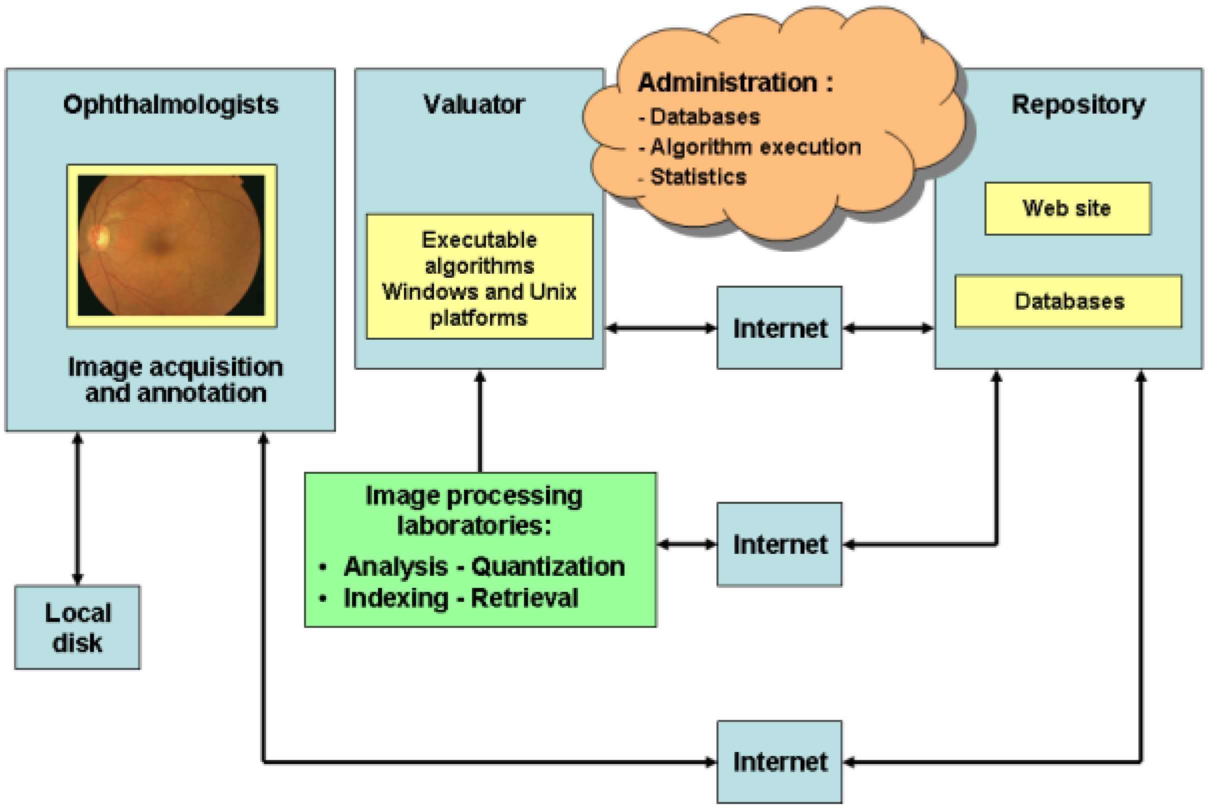


Figure 17. MESSIDOR repository architecture

MESSIDOR has a total of 1600 fundus images that was captured from 3 different ophthalmologic departments with a video fundus camera “3CCD” retinograph with a 45 degree FOV. All the images are in large size and can be studied at a very fine details. Also the dataset has diversity in a way that half of the images were taken without the pupil dilation which is the process of dilating the pupil prior to obtaining the retinogrpah. Other half of the images were taken without injecting the eye for pupil dilation .

The dataset provides with a variety of the image that belong to different scales and severity and of different subjects with different age groups. The dataset also provides the scale on which we can distinguish the cases of the patients on the severity of the disease. The scale describes the evidence of different lesions such as micro-aneurysms, hemorrhages, neovascularization, etc. and corresponding nature of the disease and risk of the progression. The scale of macular edema is also provided with the inclination of the existence of hard exudates inside the macular region and corresponding severity and risk of progression is also given .

The dataset is divided into training and testing samples for improving the existing algorithms to discriminate the cases on the scale of severity. The expected outcome of this repository indexing is to convince ophthalmologists to practice the provided algorithm and collaborate between other parterres to peruse the examination using the provided study.

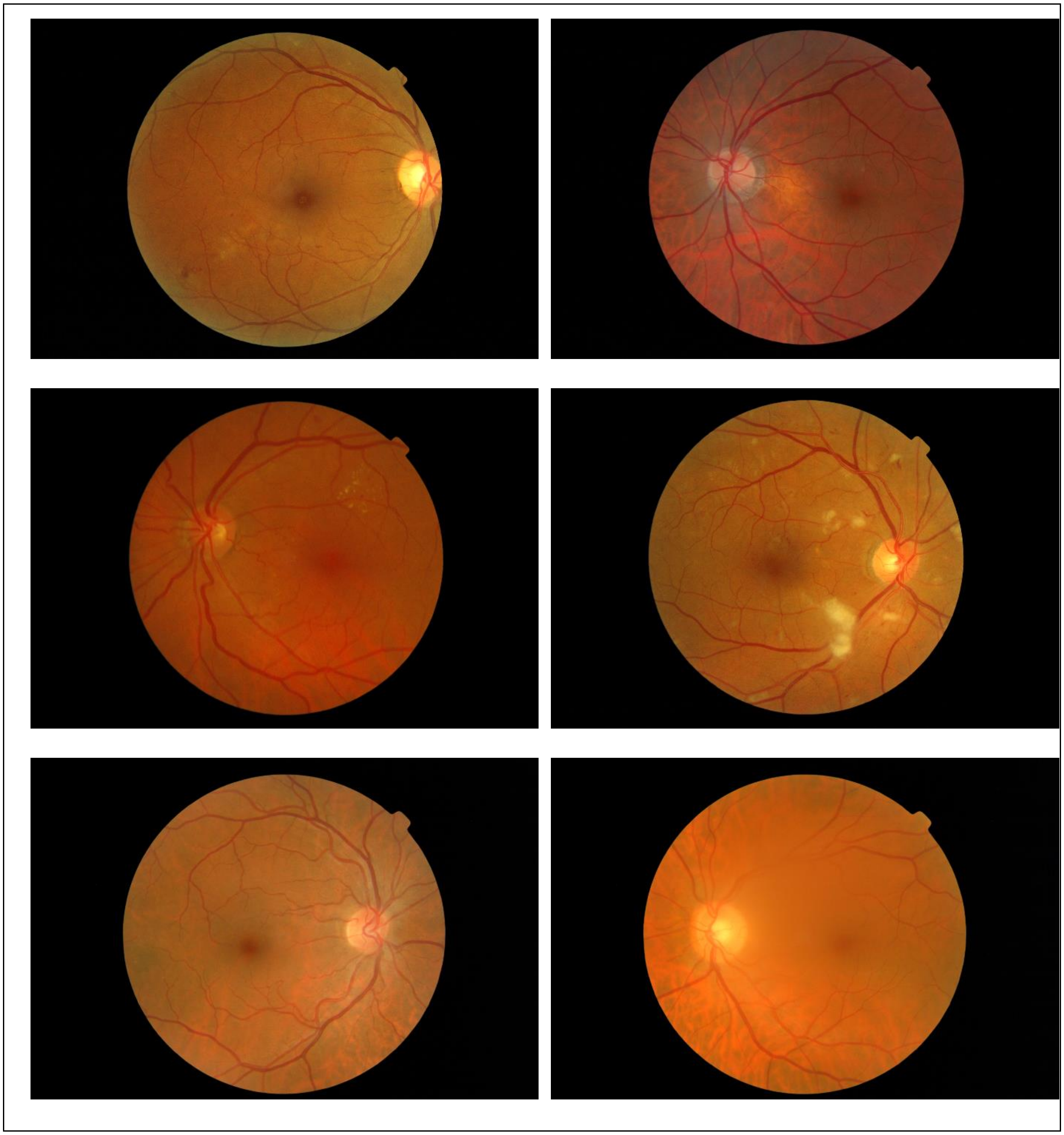


Figure 18. Variety of Images from MESSIDOR

4.5 E-Ophtha-EX

E-Ophtha is a dataset established for scientific research in the diagnostic of retinal diseases from the fundus photographs. The group worked for the designing of the dataset was OPHDIAT a tele-medical network that worked for the diabetic retinopathy diagnosis and screening. The network was employed by the ANR-TECSAN-TELEOPHTHA that was funded by the French Research Agency .

This dataset is basically consisted of two different datasets with entirely different scope and approach to deal the diabetic retinopathy cases. One is E-Ophtha_EX which only deals with the diagnosis on the basis of the exudates. The other part of the dataset is E-Ophtha_MA which is to determine the progression of diabetic retinopathy on the evidence of micro-aneurysms. On the course of our research perspective, we only focus the prior E-Ophtha_EX dataset which is composed of 82 images including healthy and diseased image for better distinguishing the cases .

The support provided with the dataset is very comprehensive. The dataset has also provisioned to have annotated regions of the lesions from multiple ophthalmologists which greatly influence the automated nature of the diagnosis. The lesions are annotated so precisely that we can grade the images on the level of severity very easily. In order to make a computer vision scheme, it is very crucial to have ground truth or annotation very precisely to make sure the nature of the lesions' attributes.

A number of researchers have used this dataset for the computer assisted diagnosis of diabetic retinopathy. It has very unique piquancy of the data that the contextual information is very evident in the whole dataset. 30 groups were working in the network that have put in their efforts with their own equipment to contribute to the dataset. The trained professionals were hired to accomplish the acquisition and marking the annotations under one protocol . The images are of varying nature and of variable people belonging to different age group. A few images with annotation are provided here for reference.

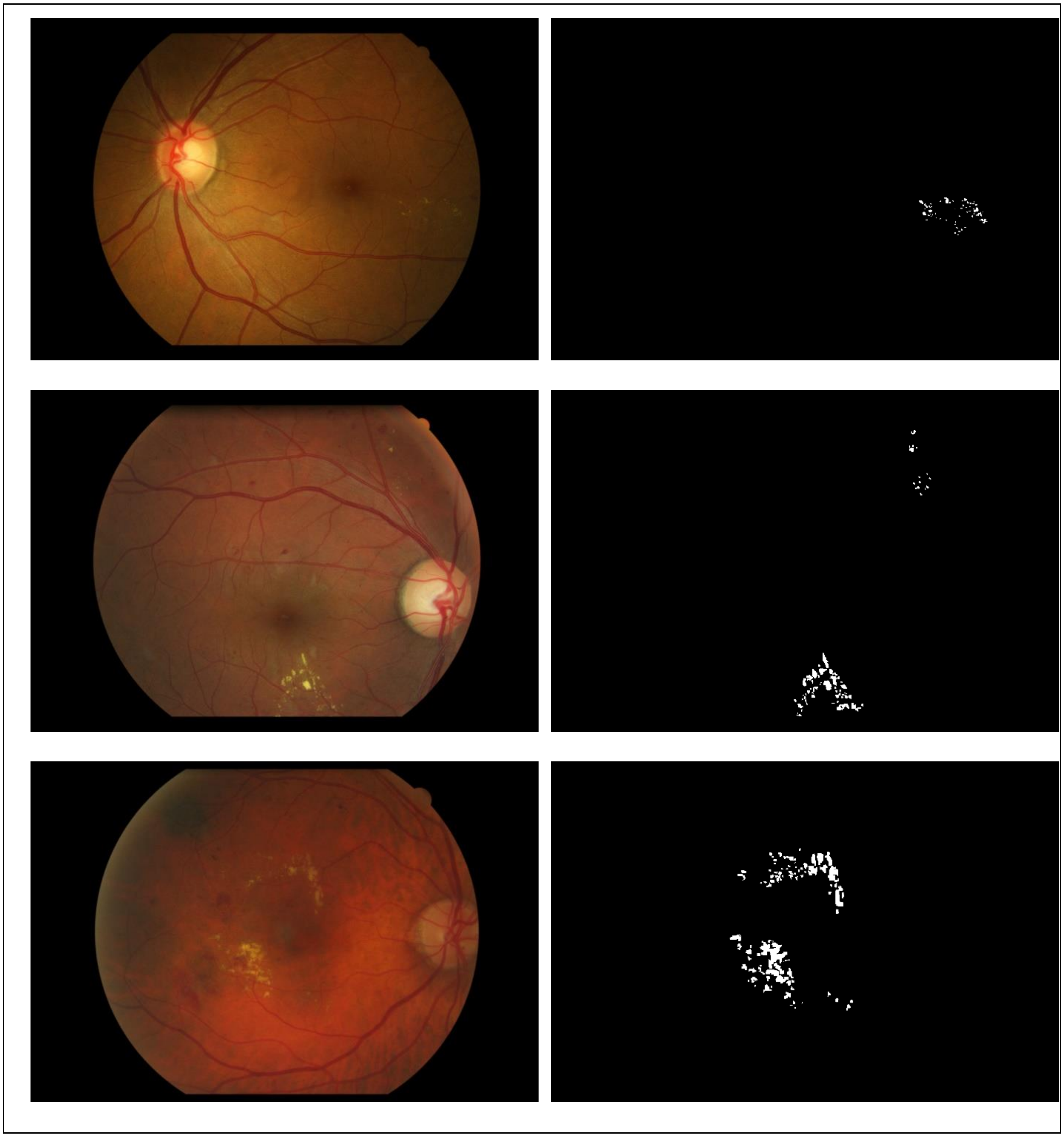


Figure 19. Images with Annotation of Exudates from E-Ophtha_EX dataset

In the end, we provide the list of materials with descriptive features of the datasets we used in our research. The comparison is provided in the table 8, where each dataset is entitled with positive and negative cases, the quality of image and the coverage of the progression of disease.

Table 8. Datasets included for Research and the descriptive features of each Database

Features		DIARETDB0	DIARETDB1	MESSIDOR	HEI-DMED	e-OPTHA-EX
DR Diagnosis	Negative	47	34	400	30	35
	Positive	73	11	800	139	47
Quality of Images	Poor	8	14	530	14	36
	Good	17	29	500	105	32
	Excellent	95	2	170	50	14
DR Grade	Type 1	32	7	430	48	31
	Type 2	38	3	296	52	4
	Type 3	3	1	274	39	12

Chapter

5

5 Results

Diabetic retinopathy is primary retinal disease in the people suffering from diabetes in the later part of their age. The fundamental part of supplying the computer assisted aid in the diagnosis and prevention of the diabetic retinopathy is to incorporate computer vision techniques to implement on the imaging data available for the research purposes. We have provided with the scheme of the implementation of the research and given the materials that have been gone through in the phase of development of the algorithm.

Certain efforts have been put up in order to provide simulated capabilities of diagnosing the patients with possible menace of developing diabetic retinopathy in near prospect. We have given the details of the scheme that has been undergone in the entire phase of the development. We have also provided the analysis of different techniques used for achieving the same objective and have also elaborated the purpose of choosing one ahead of another.

This chapter aims at the deliberation and usefulness of the proposed scheme of research with the scale of scientific performance measures. We here provide the pictorial results depicting the effects of one phase of development on the subject image and it is quite evident that the particular action is performed in the betterment of the matter. We achieved two fold approach; i.e. to achieve the detection of exudates on the image level and to achieve detection of exudates inside macular region. First part is to diagnose the potential of developing diabetic retinopathy and the later part is to examine if the case is a progressed state of diabetic retinopathy with a risk of evolving macular edema. We provide the outcome in the fashion of the methodology and list the behavior of one method in the way of achieving the target.

5.1 Assembling and Indexing the Datasets

We have chosen four datasets namely DIARETDB0, DIARETDB1, MESSIDOR and E-Ophtha_EX that are available publically on the internet. All the datasets are quite capable to the scope of this research but the MESSIDOR is too large. As the challenges occur in the domain of processing time, disk space and machine complexities, we cannot cater whole lot of the datasets which is already composed of 16 directories.

For the two portions of our research work, we first examined the inclination of the exudates in any part of the fundus photographs. We have indexed the datasets according to the evidence of exudates and mark the images in the datasets as positive or negative. The second fold of our research is to examine whether the evidence of exudates has a similarity with the macular region. For which we have indexed the datasets on the evidence of the exudates inside macular region. The index of the later part is not given in any of the case but we have ourselves maneuvered the index by checking if the exudates are available inside the macular region from all of the positive images. Basically, we have brought up two indexes for one dataset; one is for the detection of exudates and the other is to determine the possible progression of macular degeneration.

5.2 Preprocessing

The preliminary part of stepping into the automated diagnosis through imaging is the preprocessing. This stage majorly contributing in the facilitation of the image data before feeding to the machine learning algorithms. Preprocessing techniques are cheaper and can be done swiftly. These techniques incur a drastic performance to the implementation of computer vision procedures.

Preprocessing of the images takes in different kind of techniques that are real time functions and can be performed prior to the post processing. It changes the behavior of an image and make things perceptible that are hidden before. We have implemented three pre-processing techniques to the images belonging to a particular dataset that were suited the most. There has been no reason of one choosing ahead of another because a dataset is composed of entirely different kind of data samples and cannot be considered an ideal case. In the similar fashion, we consumed different kind of preprocessing techniques that were very useful in our course of research.

5.2.1 Image Normalization

Image normalization means the local normalization of the image against itself. It greatly affects the perception of the image as it steadily distribute the intensities on the whole matrix scale. It stretches the range of intensities to full scale domain of the image. Basically we divide the image intensities by the maximum or minimum of the intensities of the image. Sometimes it is called histogram stretching where the idea is to stretch the frequencies of pixels to the entire domain.

Contrast enhancement can be done with different methods, i.e. using the contrast stretching, normalizing the image with mean value, or maximum value. Sometimes the image is not found to be very rich in contrast, so you have to stretch the intensity levels to the extreme so that the whole range of the intensity domain is used. The image however changes and does not remain the same but the useful information and features can be detected in this way. The stretched in contrast is very useful when we want to detect features that are submissive with respect to the background as we see the exudates. The figure 22 shows the usefulness of the normalization and it is depicted that how the contrast is stretched and exudates are quite comprehendible with the normalized image.

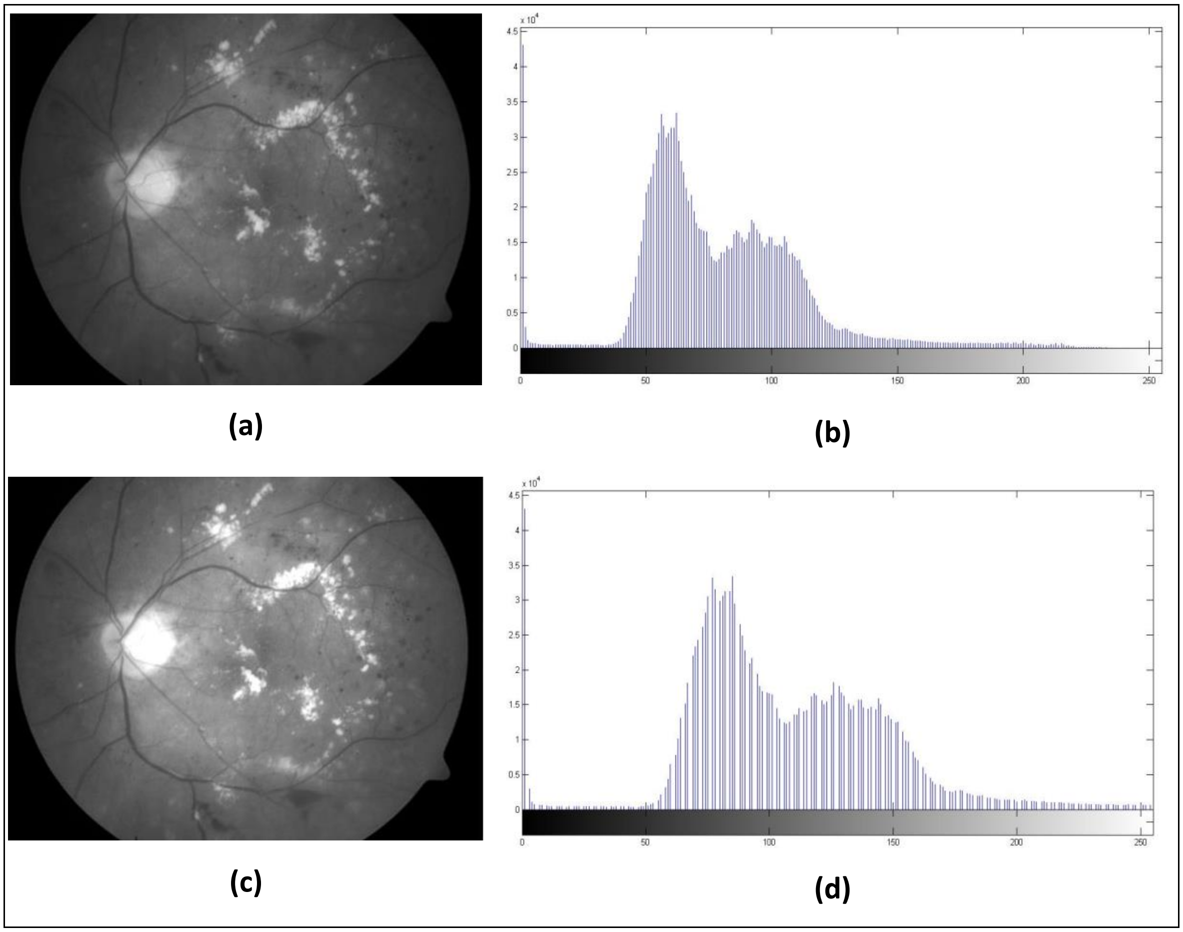


Figure 20. Image normalization (a) Image (b) Histogram of the Image (c) Normalized Image (d) Histogram of Normalized Image

5.2.2 Template Matching

This technique incurs the global normalization with respect to the attributes of the entire dataset. In this technique, a sample image is taken from the dataset with knowledge of the image being good quality and contrast. That image is said to be a normalized factor and each other image of the dataset is normalized with that reference image. This technique is used to find the regions that are consistent through the dataset.

The image that is chosen as the template does not need to be very accurate, but the contextual information should be evident and consistent as in most of the images in the dataset. The need of template matching is understandable when we process a dataset entirely separately and use the functions and select features according to the dataset.

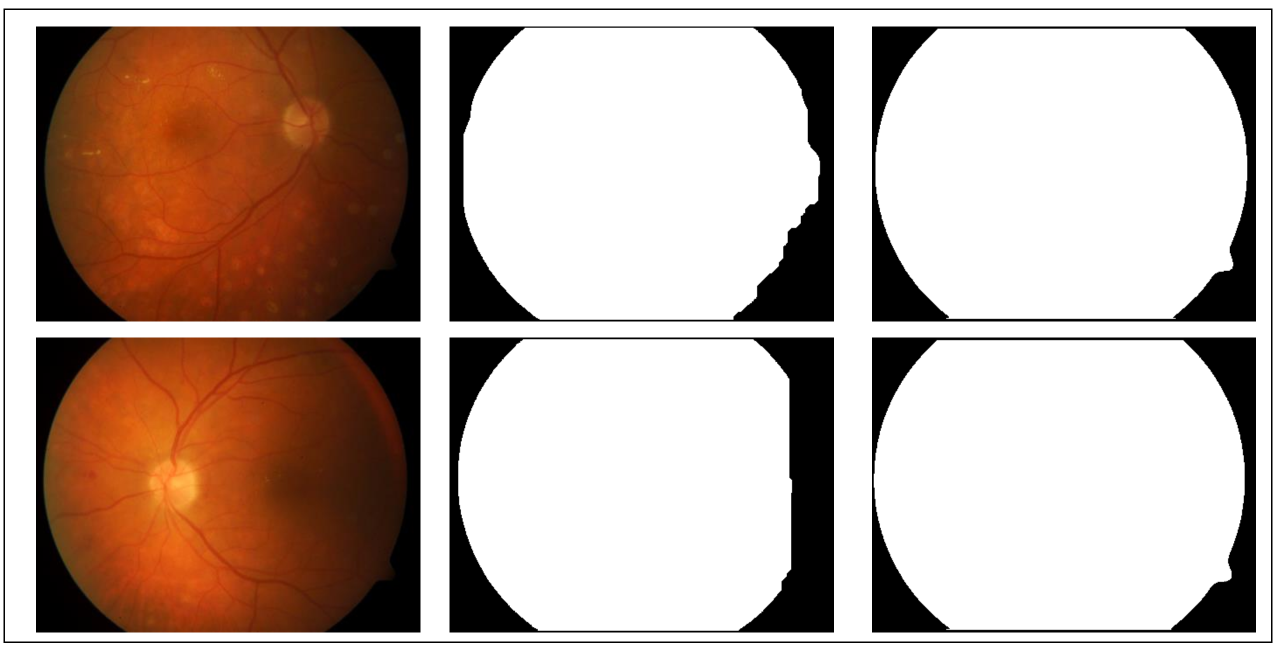
5.2.3 Non-local mean filtering

Earlier functions or techniques of pre-processing may lead in adding of some undesired noise and blares to the image that drops the quality of the image and make it difficult for post processing. We have to avoid such artifacts that could lead to wrong classification of the image. Non-local mean filtering preserves the noticeable features and provides actual information preserved in the image.

It smoothens the image without producing blur but it implies the existence of noise. We see that there are minute details that can be considered as noise, and any smoothing algorithm may cause the removal of such details. Non-local mean would remove a periodic noise that occur in the entire domain rather than a local window of whatever size.

5.2.4 ROI Segmentation

ROI segmentation means the masking out the interested region; in our case the retina we call the background mask. We have done the background segmentation with iterative area opening and hole filling from the green channel of the image.



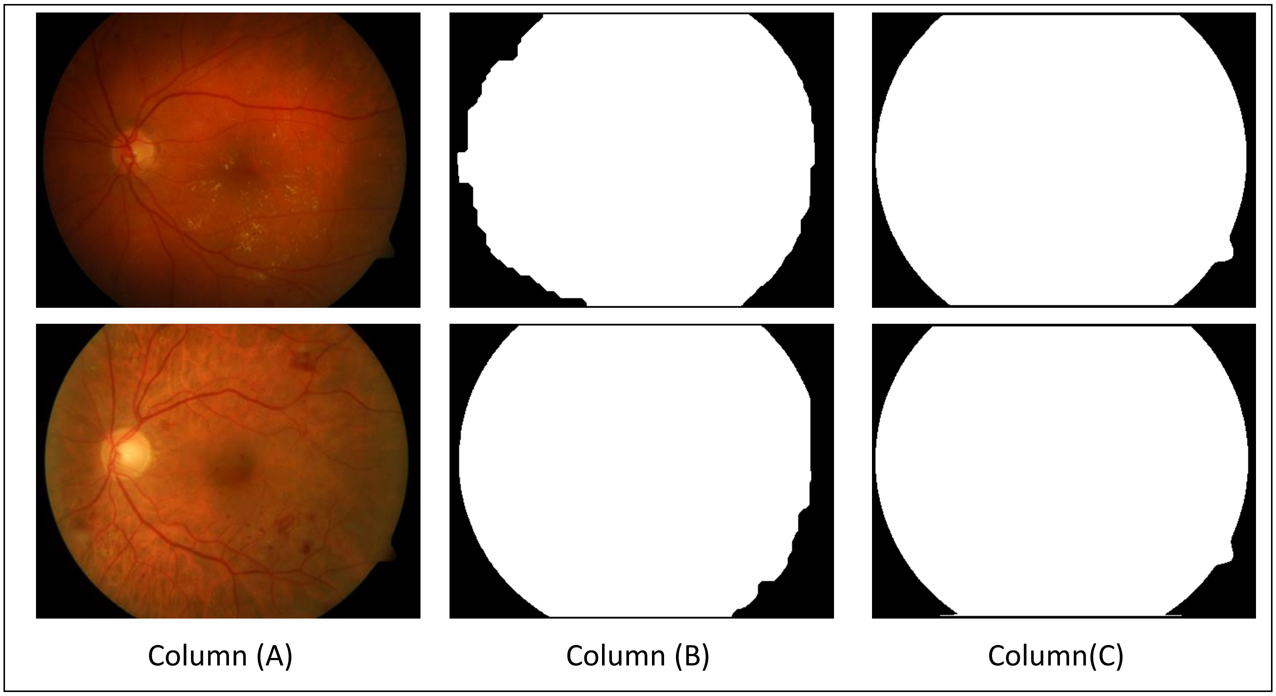


Figure 21. ROI Segmentation, Column (A) sample images from DIARETDB0, Column (B) Background mask provided with the dataset, Column (C) ROI segmentation using proposed method

5.2.5 Anatomical Features Extraction

To completely understand the clinical indicators of the retinal deformities, we need to recognize the anatomy of the retina. Since the course of our research is to find exudates and based on the exudates, we tend to find the possible erecting of diabetic retinopathy. Anatomy of the retinal images are the underlined acquaintance we need to have in order to accomplish certain tasks related to the automated detection using computer vision technologies. For which purpose, we separately define and implement algorithms for detection of those anatomical structures. We here elaborate the aftermath of conducting the said function.

5.2.5.1 Blood Vessel Detection

Blood vessels feature as one of the most important anatomy in the retinal images as it clearly defines the occupancy and coexistence of different features. It can be seen as a road map of the city where different other features such as optic disc, macula, etc. are the testaments. We have achieved vessel bank segmentation out of the retinal images with the help of Fourier and wavelet analysis together with spatial filtering.

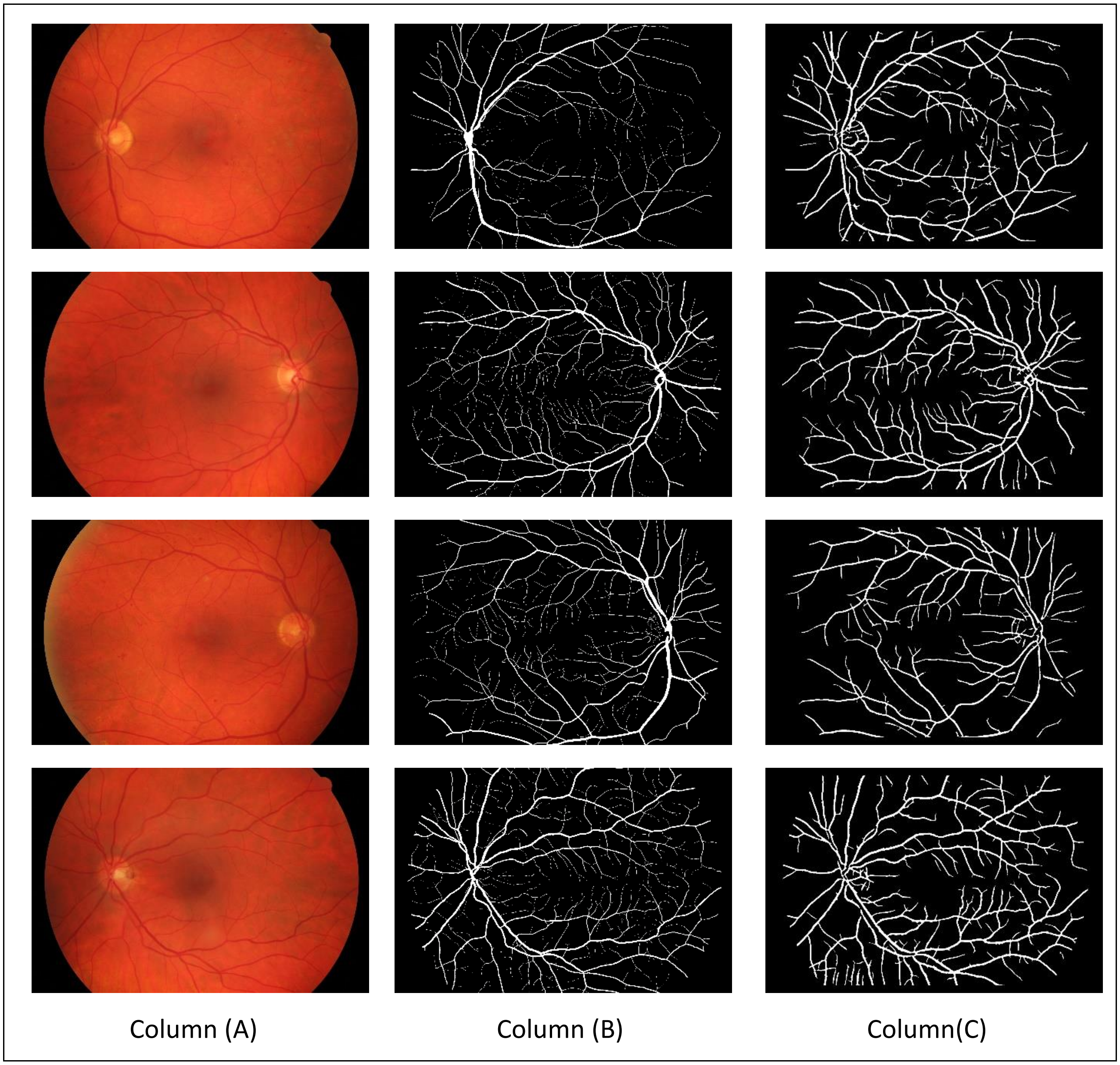


Figure 22. Images with the Vessels, Column (A) Sample images from DIARETDB1, Column (B) manually marked vessel bank, Column (C) Vessels Segmented by our method

5.2.5.2 Optic Disc Detection

Optic disc is considered to be quite an interference in our course of research as we seek to find exudates which are brighter same as optic disc. Optic disc is a consolidated part of the retina and is very optimistic in the shape, size and formation. Using the knowledge from the given attributes of the optic disc, we have flourished the location of optic disc with a high accuracy.

Location the optic disc would briefly do the task for us as we do not need to completely part the optic disc region but we need to eliminate the region around the detected optic disc center. We can easily make a mask around the center of the optic disc and eliminate the region. Doing so, we confiscate the conflict between the exudates and optic disc being brighter elements and optic disc being wrongly detected as exudate would not happen.

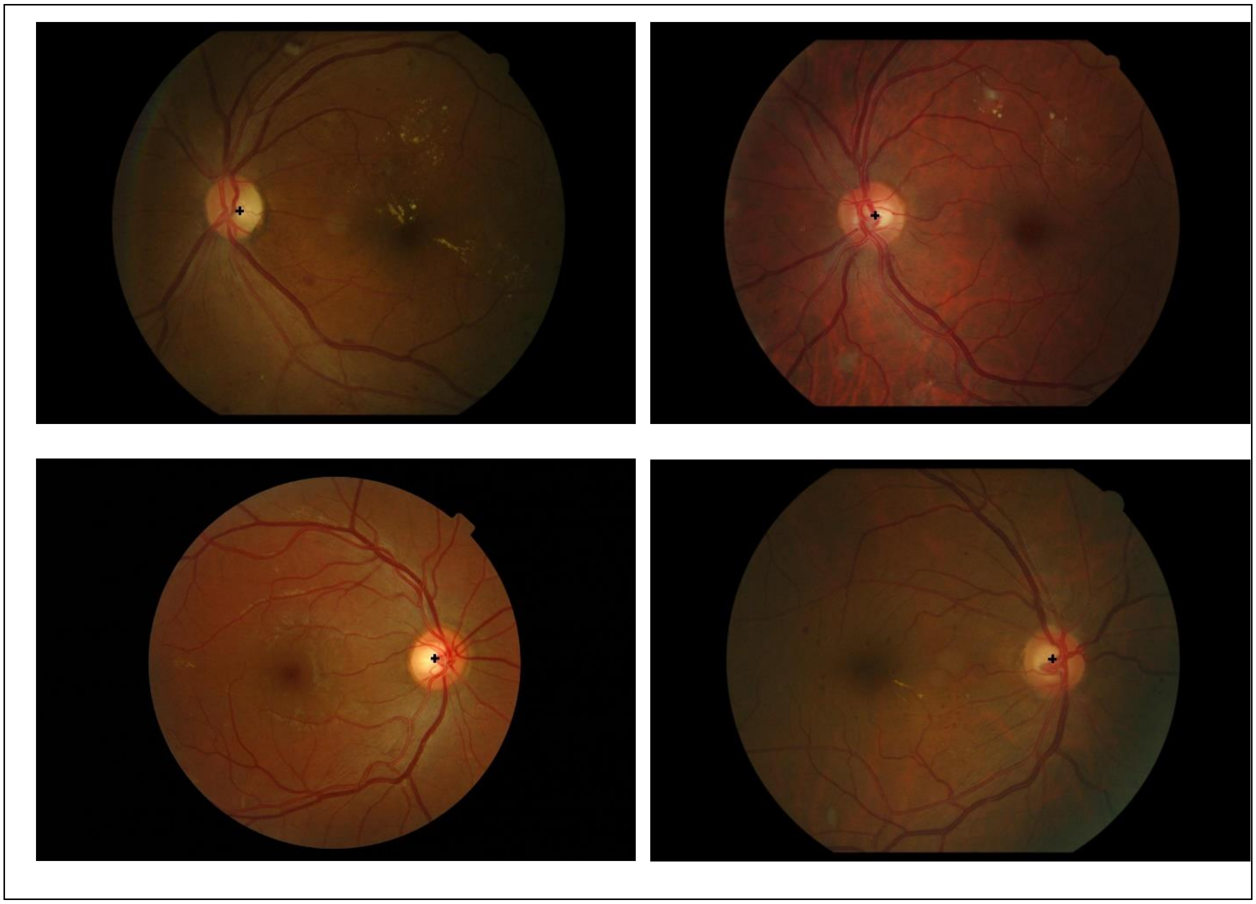


Figure 23. Images from E-Ophtha_EX with Localized OD marked by a + sign

5.2.5.3 Macula Detection

The macula is the central part of the retina and have a distinctive significance in screening of patients with diabetic retinopathy. The right detection of macular region simulates the true classification of a progressed state of diabetic retinopathy. We have detected the macular region for the later part of our research where we need to find similarity between the extracted exudates to the detected macular region. The attainment of the macular region detection is deliberated in the figure 24.

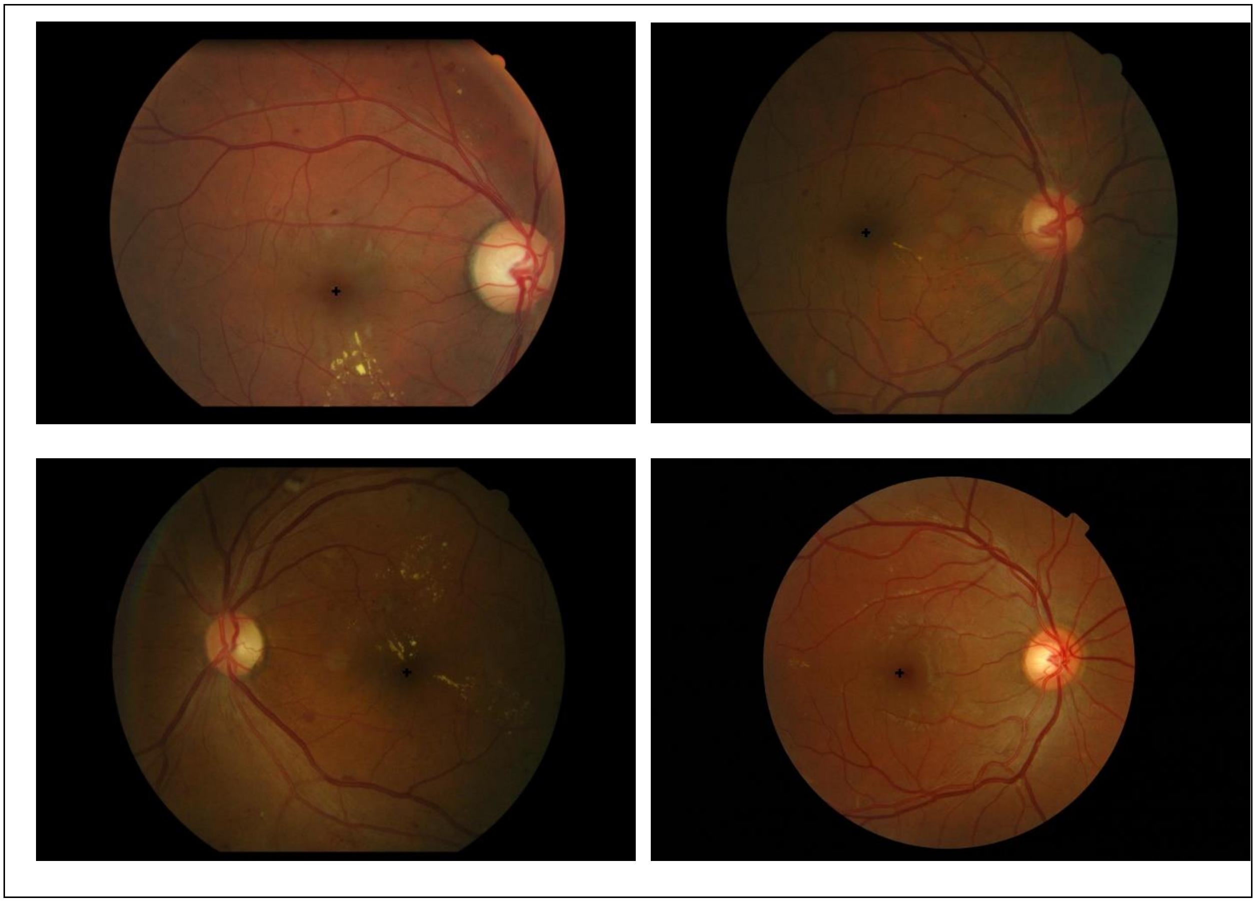


Figure 24. Images from E-Ophtha_EX dataset with Macular Region detected and marked with a + sign

The macular region and optic disc are primitive features in our course of research as they tend to deliver the contextual information as well as the anatomical rejection with respect to the evidence of the exudates. Since we are only concerned about the manifestation of exudates, we can define the interested region that are clearly out of the context.

This information is derived from a series of literature review in which it is emphasized that the contextual meaning of these features has nothing to do with the manifestation of exudates. Here we provide the optic disc and macular region both detected by our algorithm with quite a high accuracy.

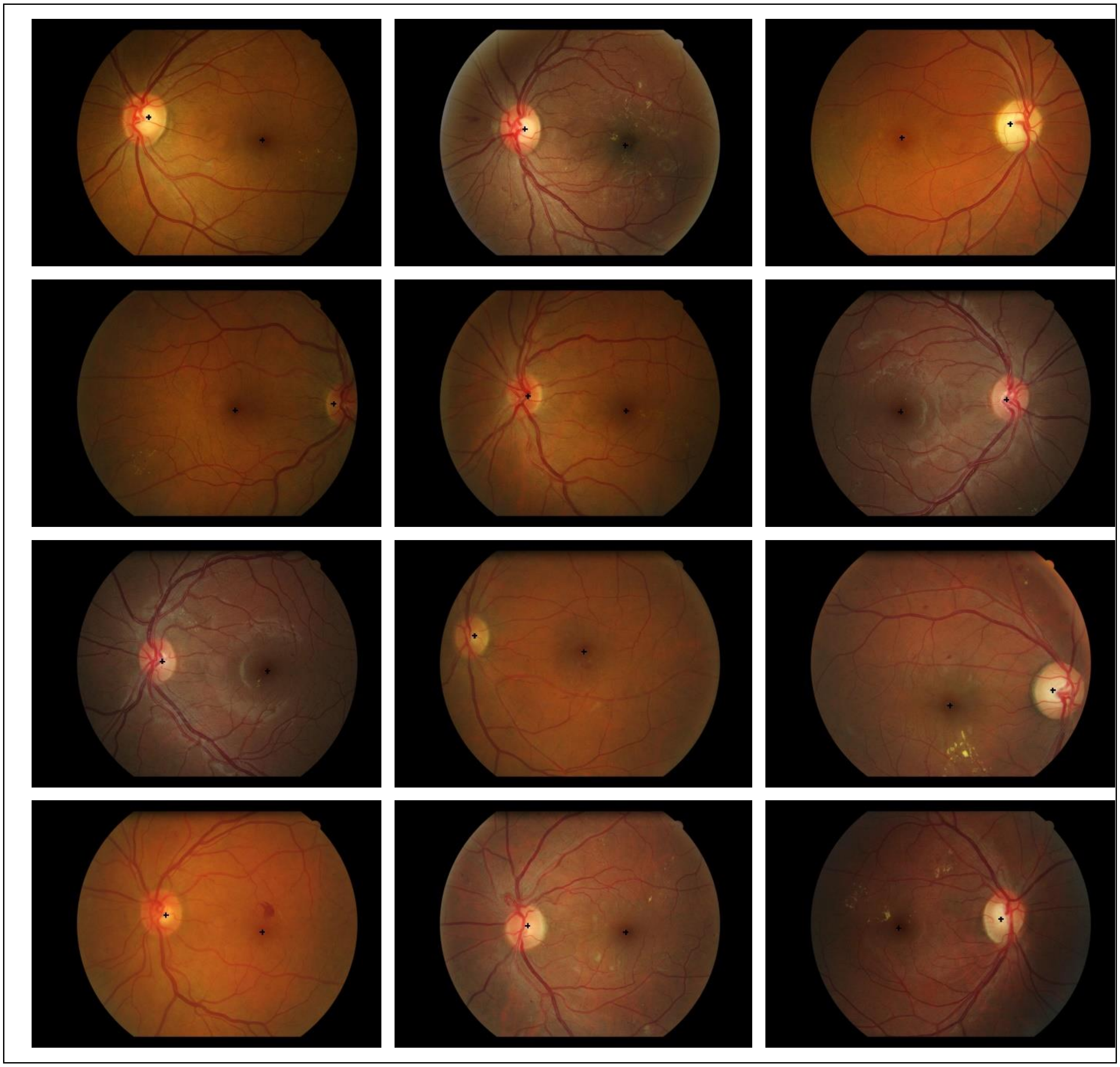


Figure 25. Images from E-Ophtha_EX with OD and Macula Detected and Marked

5.2.5.4 Main Vascular Arch Detection

With the detected vessels, optic disc and macula, we can now proceed to eliminate a critical part of the image which is vascular arch. Vascular arch is the significant part of the retina which majorly is composed of retinal vessels that works for the blood control and nervous triangulation to the brain. Blood vessels do the blood control while the optic disc is the injection point of the optic nerve that is responsible for the interpretation of the scene.

Now the vascular arch would be somewhat like the figure 26; this is to the either side of optic disc with positive and negative approach towards macula.

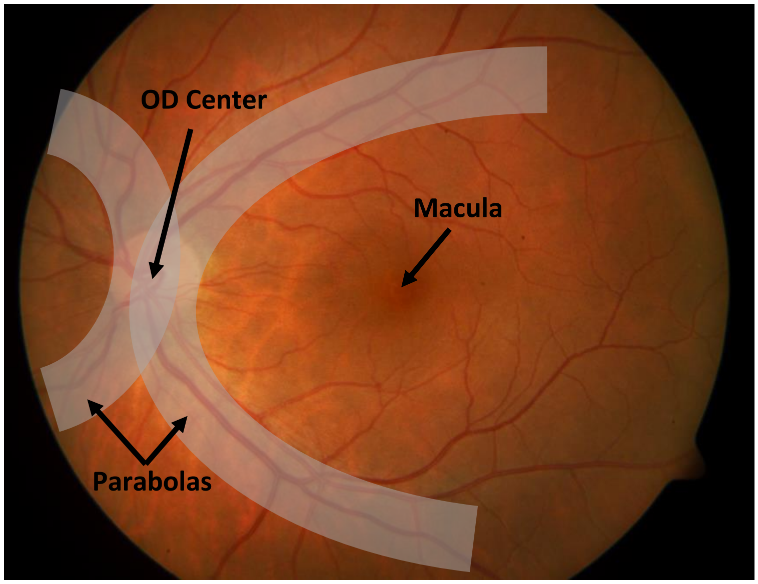
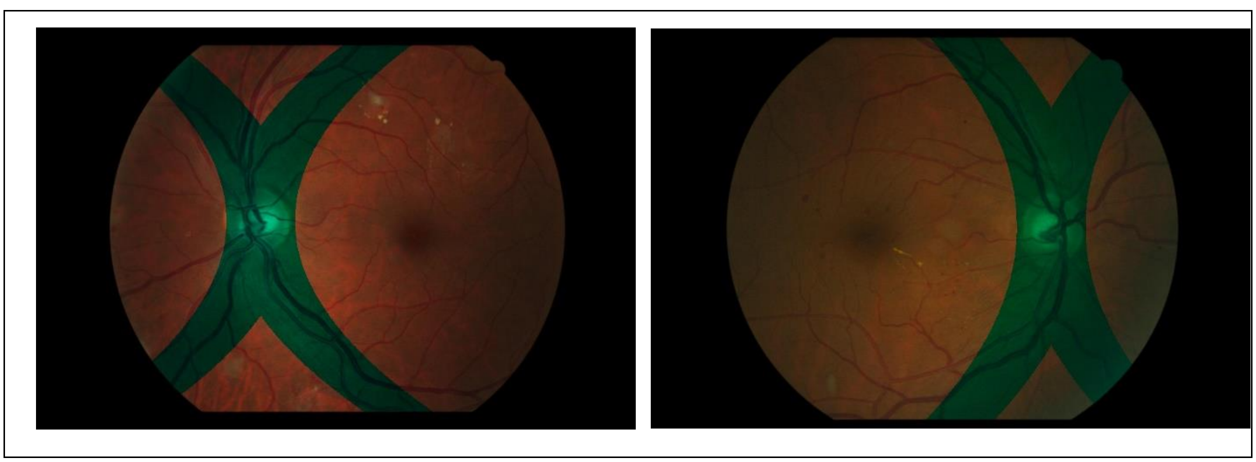


Figure 26. Vascular Arch with respect to the Optic Disc and Macula

Fitting the equation of the parabola, we easily have detected the vascular arch which perishes off the optic disc as well. Eliminating the vascular arch brought significance improvement in the latency of our exudate detection.



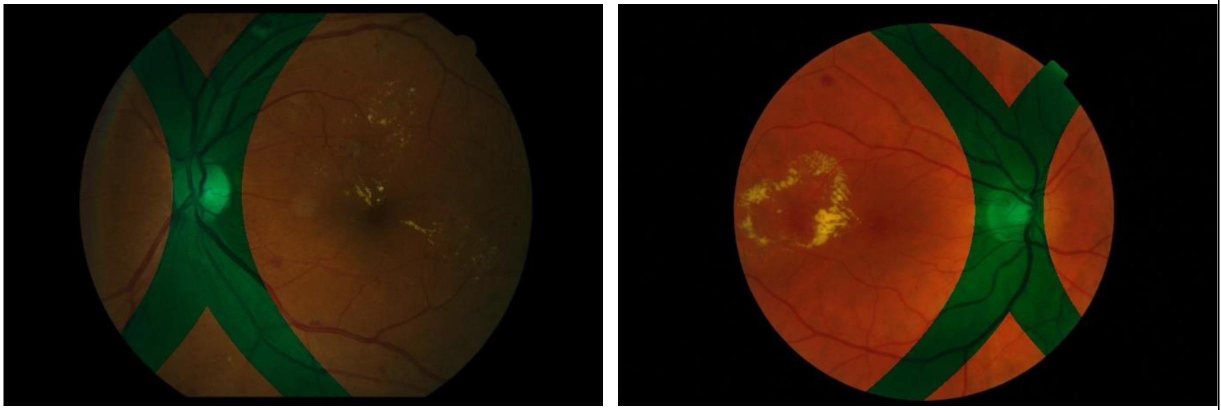


Figure 27. Retinal images with parabolas marked as the regions to be eliminated

Now, the anatomical structures are indexed and the regions where we cannot find the exudates are marked as the secondary negative mask. We are now through to the detection of exudates from the remaining regions of the retina. The further processing will come under post processing.

5.3 Post-Processing

We have now reached to the phase of post-processing that is anything comes after pre-processing. Pre-processing enabled us to bring the data in a simpler form so that the execution of the objective could be delivered better as it transforms the data into much regularized patterns that can be comprehendible for the computer vision algorithms. Post-processing lists the extraction of exudates using the morphological operations and image based segmentation. The later part of the post-processing is the participation of computer vision algorithms to add artificial intelligence flavor to the course of research. It also qualifies the research to be indexed against the research already done.

5.3.1 Exudate Detection

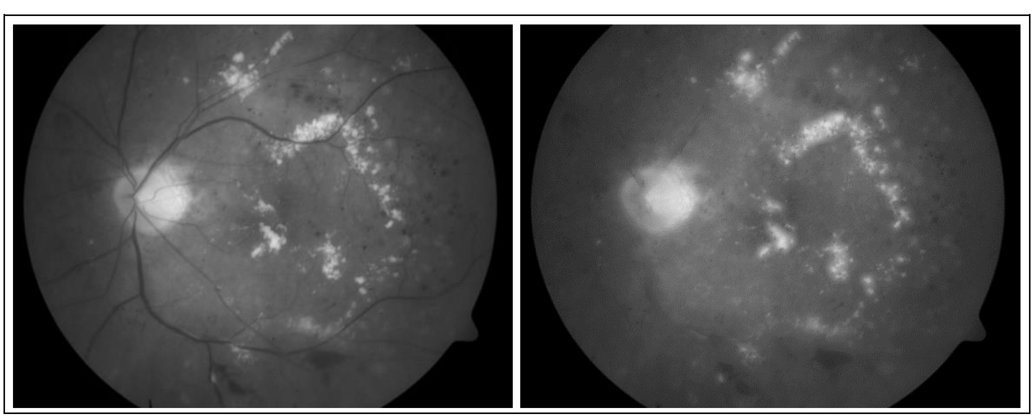
Retinal exudates are primary lesions of diabetic retinopathy that is a result of leakage from the blood vessels inside the retinal. The patients of diabetes with the passage of time loosen up the strength and the retinal vessels became weaker resulting leaking of edema onto the retina on different positions. The exudates, the count of exudates, position of exudates and the formation of exudates articulate the type of disease and the severity of the disease.

We are discussing about the detection of retinal exudates appear in a particular retinal image comes as a suspect. On the basis of that detection, we screen that particular case for either a negative manifestation of the disease or sings of the disease and expected progression of the disease. We take lead from different image processing algorithms as well as machine learning techniques to incur the objective function. We list the outcome results at each level of post-processing.

5.3.1.1 Vessel Inpainting

The exudates can be considered as the striking objects that empirically respond to the gradient function. The other object that indicates the same behavior in the fundus image is the blood vessels bank. We have already materialized the retinal blood vessels and carefully extracted out the blood vessels. On the basis of the blood vessels, we can smooth the regions of the fundus image that are capable of responding to a gradient function.

Cracking the turbulence need the extraction of the blood vessels from fundus image so that it does not leave any significant hit when we apply gradient functions. Only way out to the said objective is to inpaint the regions where there are blood vessels. We have implemented the vessel inpainting in the Fourier domain with simply normalizing the fundus image to the vessel bank. The result of vessel inpainting is quite exception when we see on a graphical statute.



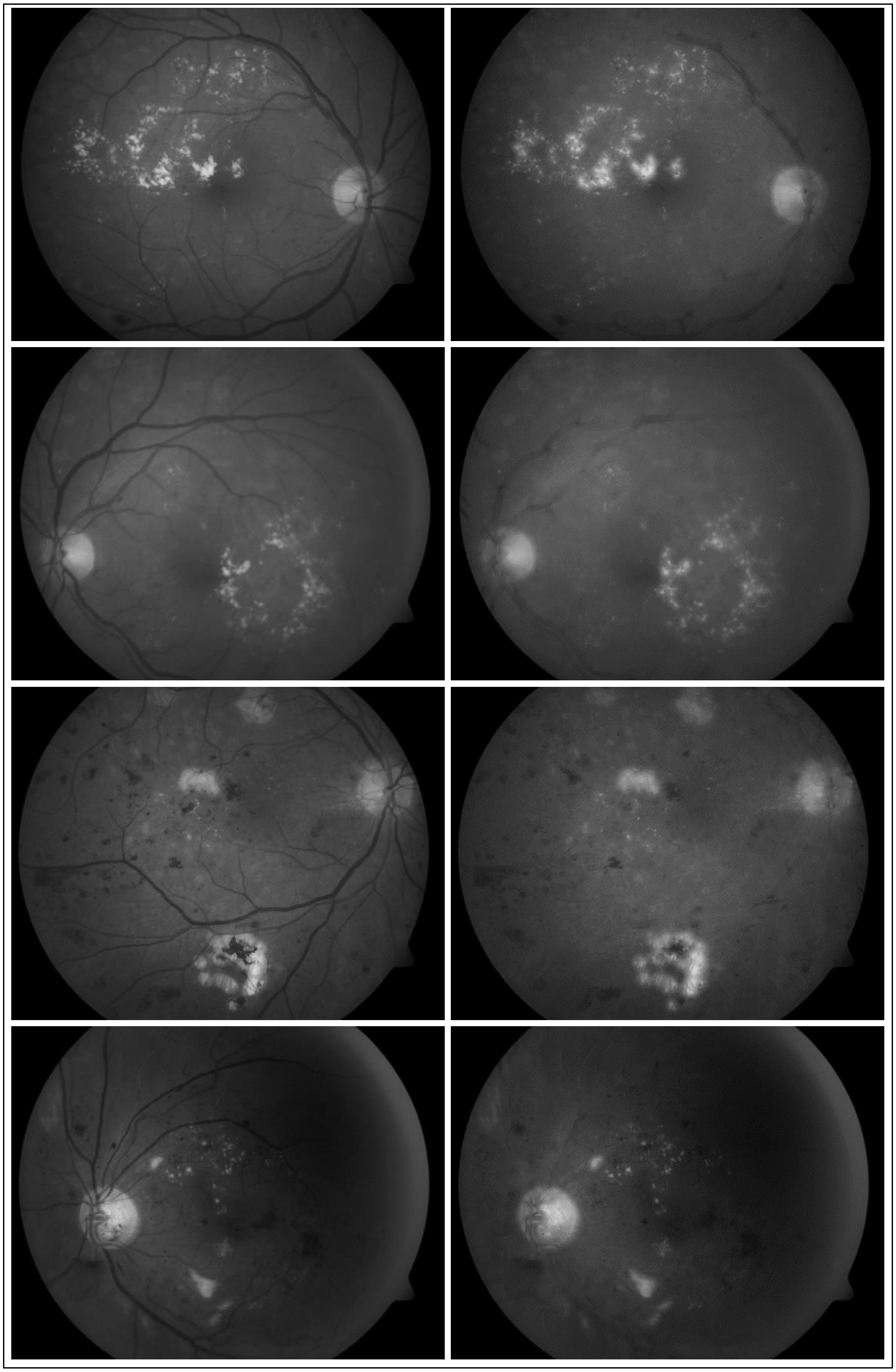


Figure 28. Vessel Inpainting effect on images taken from DIARETDB0

5.3.2 Candidates Extraction

In this section, we present techniques used for the extraction of candidate regions that suit fit for a possible exudate. The morphological operations are used for the said purpose out of the vessel inpainted images. The candidate extraction is a two-fold process where we dissect the process in extracting the larger candidates and the minute candidates. Since the exudates can have variable size, the larger candidates are quite easy to find and minute or finer candidates are extracted in fine level analysis. For the larger candidate extraction, we used Gabor filtering that nearly does the job for us.

5.3.2.1 Coarser Analysis

For the analysis of the exudates, it is suitable to find the exudates at the coarser level for screening purposes. The reason for this is if the patient has tendency of developing diabetic retinopathy, the exudates would come in larger size that would be annealed by the coarser level analysis of the patient image. Otherwise, a finer level detection is also necessary for finding out the minute manifestations of the exudates to estimate the future progression of the diseases which are in the earliest stages.

At the coarser level, we extract the candidate exudates by the means of gradient filtering where we define gradient by the step change in the window of the filter. The gradient filter response would give us the local maxima in each window where the window is sliding right to left, top to bottom. We used column wise process to record the gradient variation with a variance filter. A careful thresholding gives us an estimation of the regions where the exudates would be concentrated. It would however leave some holes as for the larger exudates would reserve the filter response in its region and does not respond to the variance filter. An area filling with holes would give us the concise approximation of the candidates. The reconstruction would also done the same job for us but it would also pick the non-relevant parts of the image and boosts the response. The result of this step is exhibited in the figure 29.

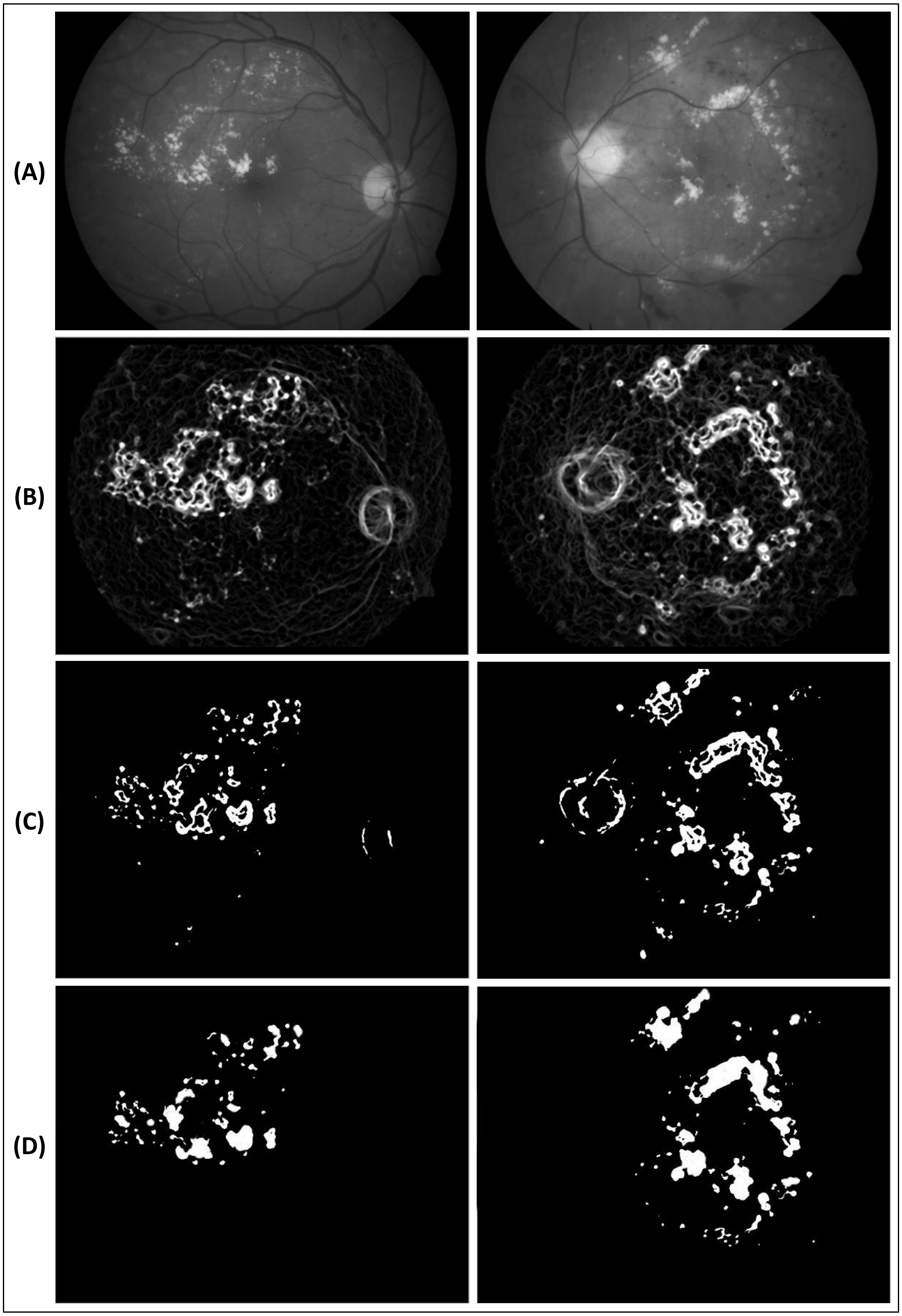


Figure 29. Result of Gradient Filtering. (Row A) the green channel image (Row B) Response of gradient filtering (Row C) thresholding the filter response (Row D) applying the parabola mask to avoid OD regions and hole filling

5.3.2.2 Finer Analysis

For the small exudates, we analyzed the inpainted images for finer details so that the smaller exudates may not be left untreated. We did that with morphological reconstruction by filtering the image with much smaller structuring element and then applying top-hat reconstruction. The result of the fine level analysis is given in the figure 30.

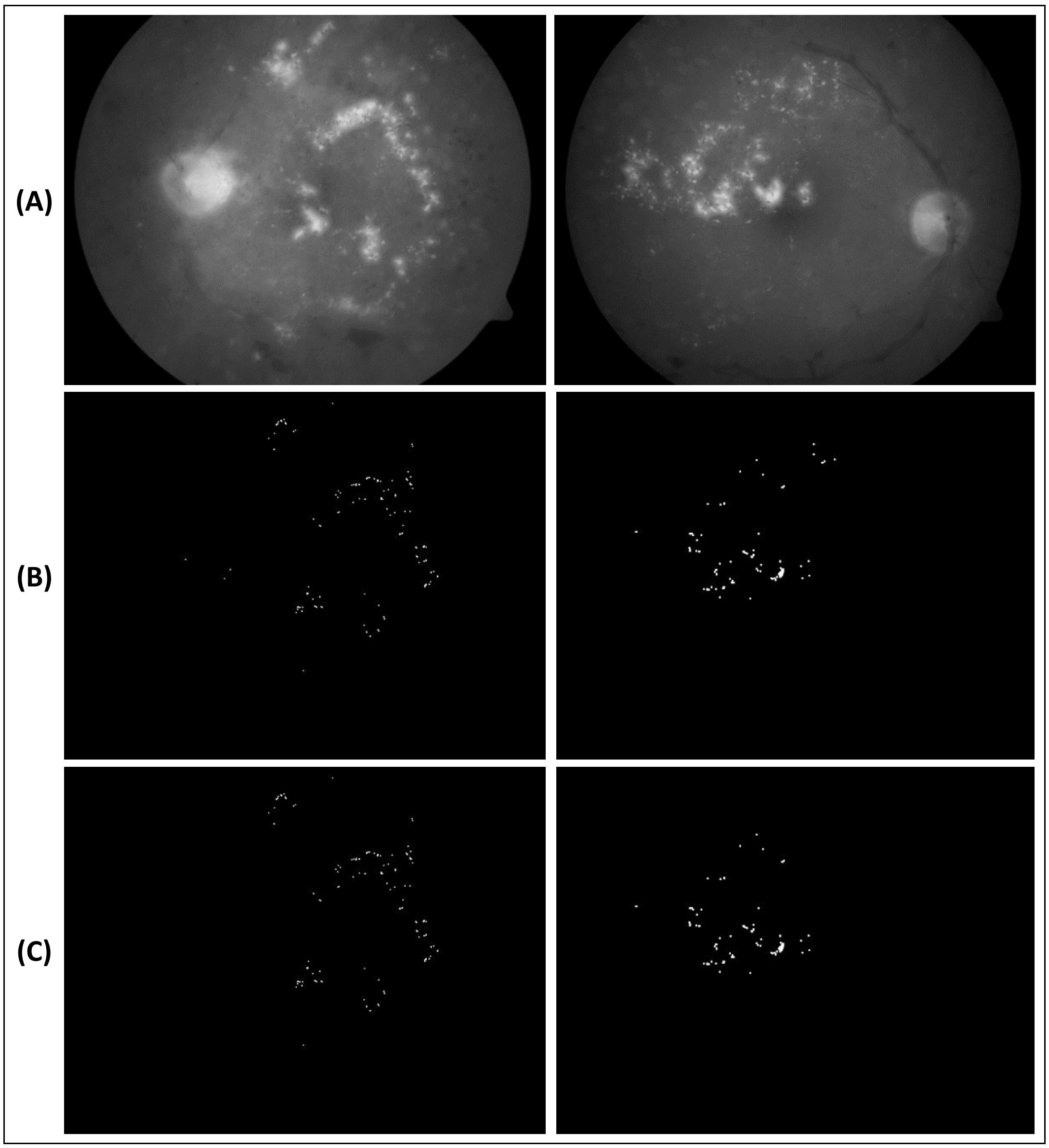


Figure 30. Result of Fine level Analysis. (Row A) the inpainted green channel image (Row B) Response of morphological reconstruction (Row C) applying the parabola mask to avoid OD regions

5.3.2.3 Final Selection of Candidate Exudates

Final selection of the candidates would have both coarser level candidates and fine level exudates combined with the union of the two resultant responses. That is produced by taking the supremum of the two responses. The figure 31 shows the combination of the two resultant responses and it is quite evident that how the boundaries of the regions is appropriated by two level extraction of the candidates.

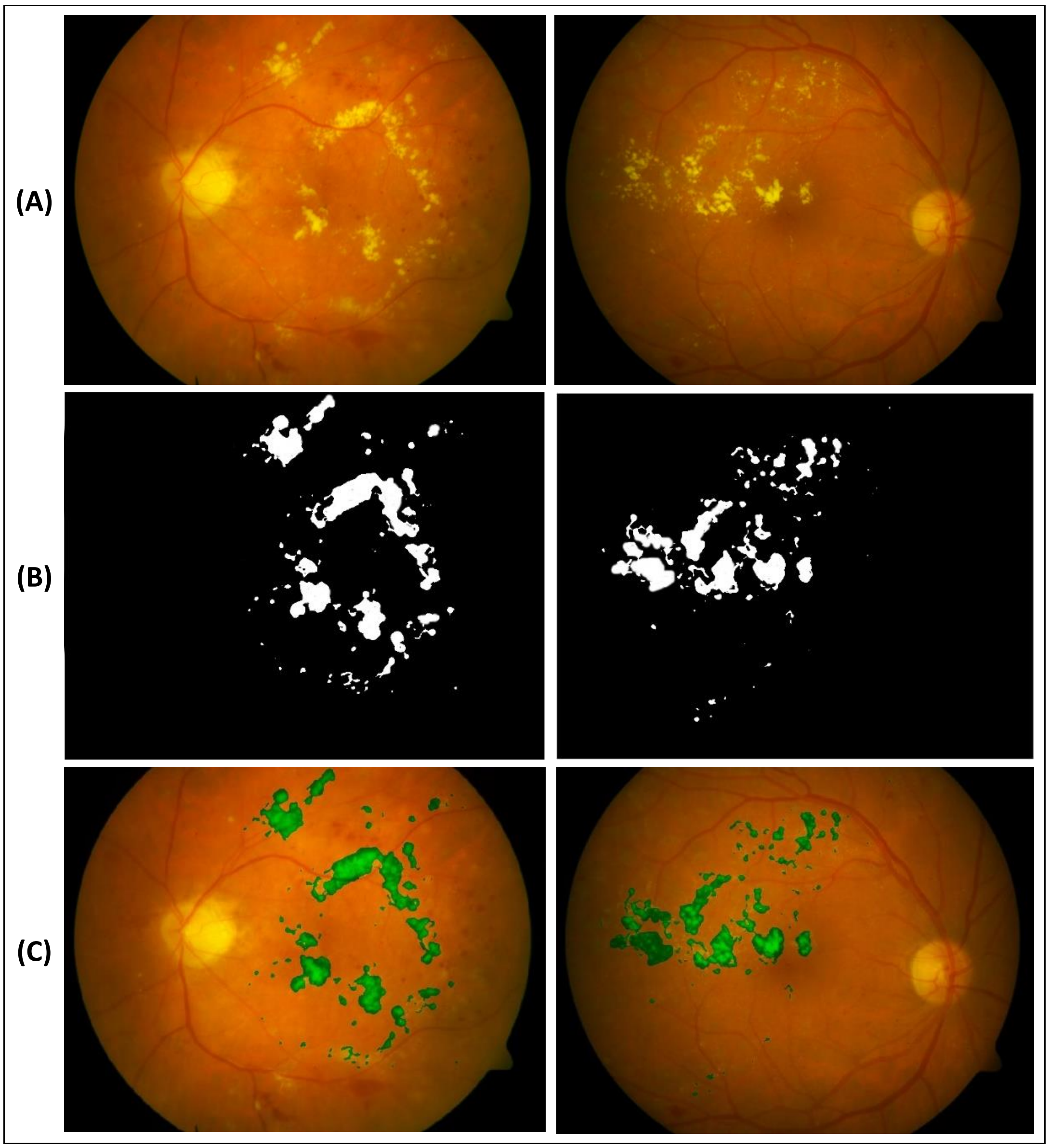


Figure 31. Final Result of Candidate Extraction. (Row A) the original image (Row B) Supremum of coarser level and finer level analysis (Row C) superimposed exudates on the original image

5.3.3 Performance Evaluation

For the scientific performance evaluation, we present the statistical measures after performing support vector machine classification of the true exudates with specified feature set. We have established the screening ground truth for exudate images as well as images with diabetic macular degeneration. The ground truth of each dataset is based on a column matrix with the corresponding values to the dataset images represented either positive or negative. The positive marked images are those where the exudates are evident and marked negative otherwise. Selection of the candidate exudates have been fed to the support vector machine which classify the candidates either a true exudates or false depending upon the descriptive features out of the feature set we have established.

5.3.3.1 SVM Training and Testing

We used support vector machine for training our model with the radial basis function. The feature set for training is composed of 1215 elements, each of 24 features. The biasness of the SVM is retained as 33%. Candidate exudates selected in the previous section are labeled and supplied to the SVM for classification under the learned model. The classification was rendered with either positive or negative corresponding to the evidence of the exudates in the subject image. The response of the SVM classifier is indexed for scientific performance measures.

We used standardized scientific measures for the recognition of our research as the common practice suggests. We usually find or make the ground truth for the data ourselves for the training and indexing purposes. The same function is used for the tracking the performance of the classifier. The principle qualification of the exudate screening method is presented by the table 9.

Table 9. Principle Scientific Measurements

	Pixels Triggered as Exudate by the algorithm	**Pixels Identified as Non-Exudate by the algorithm**
Pixels Annotated Manually as Exudate	True Positive (TP)	False Negative (FN)
Pixels Annotated Manually as Non-Exudate	False Positive (FP)	True Negative (TN)

We used Microsoft Excel for the quantification and took advantage of the transitions from the below equations.

IF(AND(GROUND_TRUTH=1,DETECTED=1),"True Positive",)
IF(AND(GROUND_TRUTH=0,DETECTED=0),"True Negative",)
IF(AND(GROUND_TRUTH=1,DETECTED=0),"False Positive",)
IF(AND(GROUND_TRUTH=0,DETECTED=1),"False Negative",)

For the quantifying the performance of the algorithm, we have different evaluation functions that describe the fitness of the algorithm. Researchers use such functions for indexing and presenting the algorithm results. There are several performance evaluation functions that can be derived from the measures mentioned in table 9. The characterization of each is given in the table 10.

Table 10. Scientific Measurements used for the Performance Evaluation

Scientific Measure	Description	Function
Accuracy (ACC)	Ratio of classified exudate pixels to the total pixels plus ratio of pixels classified as Non-Exudates to the total pixels.	(TN + TP) / (FP + TP + FN + TN)
Sensitivity (SN)	Ratio of classified exudate Pixels to the actual exudate pixels in ground truth. The same is called True Positive Rate.	TP / (FN + TP)
Specificity (SP)	Ratio of pixels classified as non-exudates to the actual non-exudate pixels in ground truth. (1-SP) is also called as False Positive Rate.	TN / (FP + TN)
Positive Predictive Value (PPV)	Likelihood of a pixel classified as exudate being an actual exudate pixel.	TP / (FP + TP)
Negative Predictive Value (NPV)	Likelihood of a pixel classified as non-exudate being an actual non-exudate pixel.	TN / (FN + TN)
False Detection Rate (FDR)	The False Detection Rate is the probability of the exudates been identified is a false positive.	FP / (FP + TP)
Area Under the ROC Curve	Mapping of fraction of True Positive Rate to the False Positive Rate or fraction of Sensitivity to Specificity on 2-dimensional plane.	TPR/FPR

The other performance evaluation function can be derived from the measures mentioned in table 10, such as positive likelihood ratio, negative likelihood ratio, etc. We provide here the competitive analysis for the detection of exudates in the scientific measures presented in table 10. We have achieved good results in all of the employed datasets and indexed the corresponding results.

Table 11. SVM Classification Measures for the detection of Exudates for all the Datasets Listed

Image Dataset	Sensitivity	Specificity	Accuracy	PPV	NPV	FDR	AUC
DIARETDB0	90.91%	94.34%	92.31%	95.89%	87.72%	4.11%	86.24%
DIARETDB1	78.57%	100.00%	93.33%	100.00%	91.18%	0.00%	95.58%
E-Ophtha_EX	97.83%	94.44%	96.34%	95.74%	97.14%	4.26%	96.44%
MESSIDOR	94.12%	87.50%	92.00%	94.12%	87.50%	5.88%	90.80%

The area under the ROC curve defines the impetus of the perfection of the algorithm. We have achieved impressive characteristics on the ROC curve. The figure 32 shows the area under the ROC curve for the datasets listed in table 11.

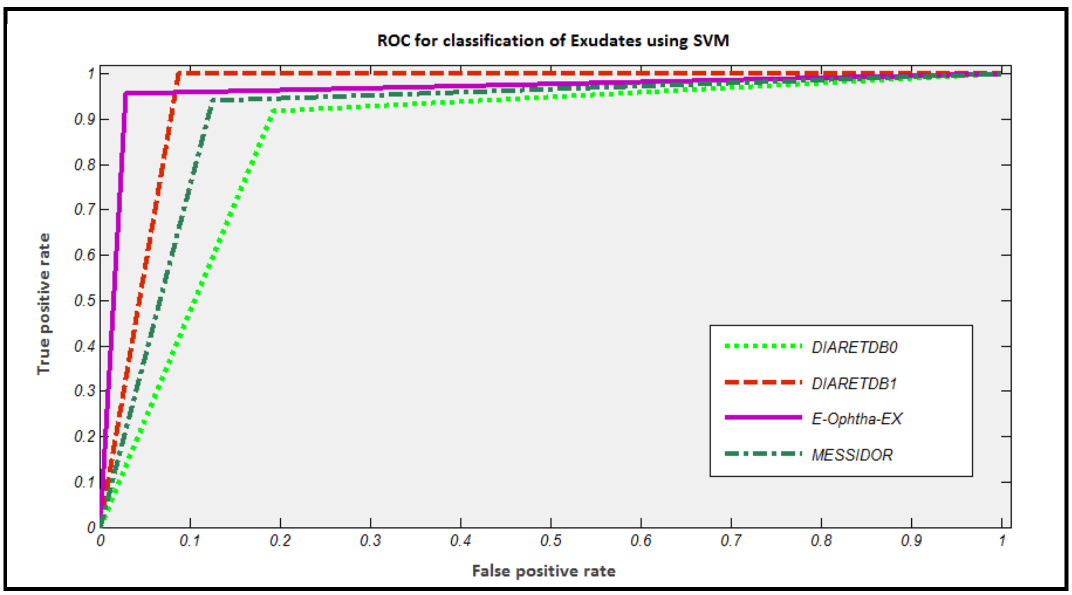


Figure 32. Area under the ROC Curve for the classification of Exudates from Different Datasets

So, we have drawn respectable results in terms of scientific measures to allow our research to be indexed in the routine of the retinal image processing for the study of diabetic retinopathy. The screening purpose of the exudates would be very effective in the screening of patients with diabetic retinopathy. We now provide the results and effectiveness of the algorithm with the inclination to the macular degeneration. In the section 5.3.3.2, we describe the results of the exudates detected inside the macular region

5.3.3.2 Results for Macular Degeneration

The macular degeneration discusses the evidence of the exudates inside macular region. Our algorithm have achieved delicate accuracy in the detection of the exudates. We simply replicate the results and compute the similarity of the resultant images with the image that is masked with macular region.

Table 12. SVM Classification Measures for detection of macular degeneration for all the Datasets Listed

Image Dataset	Sensitivity	Specificity	Accuracy	PPV	NPV	FDR	AUC
DIARETDB0	100.00%	96.12%	96.92%	87.10%	100.00%	12.90%	93.54%
DIARETDB1	70.00%	100.00%	93.33%	100.00%	92.11%	0.00%	96.05%
E-Ophtha_EX	89.47%	96.83%	95.12%	89.47%	96.83%	10.53%	93.14%
MESSIDOR	89.74%	95.08%	93.00%	92.11%	93.55%	7.89%	92.82%

Similarly, the plot of the area under the ROC curve is also elaborated here. Clearly, it is evident the algorithm performs better in macular degeneration because we have a Bayesian function here with the probability of enforcing the detection of exudates inside the macular region greatly influences the algorithm performance. That is because of the contrast apparent between the macular region and exudates.

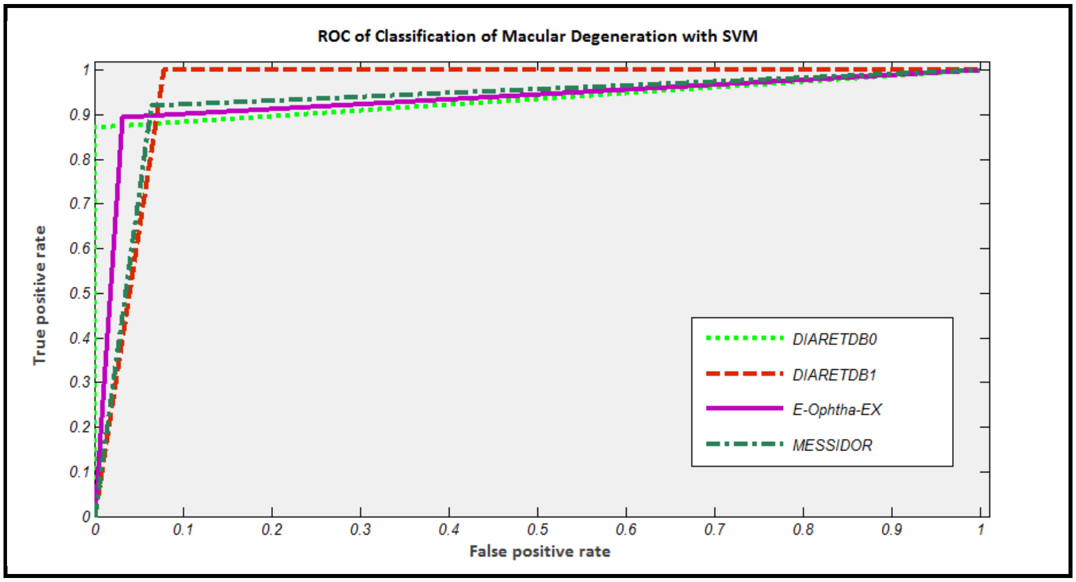


Figure 33. Area under the ROC Curve for the classification of Exudates from Different Datasets

Chapter

6

6 Discussion

The work submitted here is to imitate a screening tool for the early detection of patients with diabetic retinopathy and macular degeneration based on the primary cause; the exudates. We focused on the detection of exudates throughout the research as they are decisive lesions for the development of diabetic retinopathy. It would server the purpose of dealing with a speedy purging of the patients with a potential threat of developing retinal diseases [1].

There have been many such studies that would be equally good to be in practice for the clinical maneuvers in ophthalmology. The proposed work is confronted for the screening out the sample images for publically available datasets we have collected from the web. The images are from different sources and taken from different apparatuses. So, we would say that our proposed work would fit any image taken with the help of standard apparatus and techniques resembling the source images. In the sublime routine of our research, we conducted the mass screening with feeding multiple images from different sources to our algorithm. Our proposed work justifies the purpose of screening with a good quantitative confidence.

There are many other lesions in the retinal pathologies that are pivotal in the identification of retinal diseases. Sometimes the lesions dictates the progression of the disease with the relative severity and grade on the evidence of the frequency of occurring inside the region of concentration. We have expounded one of those lesions which stands prime in all the lesions for the identification of retinal diseases. To make it as applied as the clinical expert, the retinal screening system would have to be so much competent as to catch each and every minutiae of those lesions which is far too challenging. The scope of presented study is limited to the detection of the evidence of exudates and can be protracted for the further engineering of materialized screening with conducting other lesions.

The future work is anticipated to have precise recognition of primary lesions with the learning of the position based affinity to be able to decide for the retinal pathology, the severity and the grade. We have intensions of covering local cases with the support of acquisition of the images and screening the patients there and then through the means of connected tools of automated annealing. We tend to incorporate emerging statistical methods to better cope with the learning on a mass scale.

We used MATLAB software for the development and analysis of the subject proposed here. There are other tools that provide equally comparable results but the luxury of adopting the very platform is that it provides the frill to adjust the handholds to view the results on the plane and regulate the algorithm accordingly. A single case would take around 20 seconds in the streamline for the analysis on a primary machine Core i3, running Windows operating system and having 4 GB or RAM.

Chapter

7

7 Conclusion

The system for the early detection of diabetic retinopathy and macular degeneration is presented here. Diabetic retinopathy is characterized by the evidence of retinal exudates and the macular degeneration is considered where the exudates appear within a small portion (size of optic disc) of the macular region. Severity of macular degeneration depends upon the constituent exudates, their symmetry and frequency of occurrence within macular region. It is worth noticing that diabetic retinopathy and macular degeneration causes vision loss at different levels from ordinary to severe and preventive measures can be taken if we can find out the development in earlier stages. That necessitates an effort of conducting a study dealing with the detection of those diseases on the sign of the primary lesion; the exudates. Different authors worked for the screening of the retinal diseases but none can provide such a quality of results that it can be applied in clinical practice. We also reviewed the literature explicitly which elaborate different methods based on computerized screening and diagnosis systems for retinal diseases. We have explored recent research that has been carried out in the field of retinal image analysis specifically on diagnosis and screening of macular edema. We have come up with an effort to sum up all the literature published till date on the subject of macular edema.

We present an end-to-end mass screening methodology for the identification of retinal diseases such as diabetic retinopathy and macular degeneration. We have come up with a solution with the assistance of image processing techniques and machine learning methods. We mentioned the means of qualifying and quantifying the results produced from the research. On the same scale, we present the quantitative analysis of the proposed work to append the competitiveness against the market research. We have achieved the significant results on four of the publically available datasets; DIARETDB0, DIARETDB1, E-Ophtha-EX and MESSIDOR and achieved competitive results on the scientific measures.

We provided the impact of proposed work on the sample cases impending from different sources. We immaculate the results with the pictorial representation of the procedures adopted and signifies the importance of selected procedures against the contrary methods. The efficiency, robustness and adaptation influence is also appended in the later part. Also, the augmentation and future endeavors to the proposed work is presented.

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