

# Chapter 1

## Introduction

### 1.1 Medical Image Analysis

To diagnose a disease, we need a thorough assessment of the affected organ. With the advent of medical image analysis, the study of various organs has evolved from surgical ways to non-surgical imaging. Today we have numerous imaging modalities to capture anatomy of an organ inside the body in non-invasive manner, which medical experts can use for diagnostic purposes. Some examples of these modalities include X-ray images, computerized tomography (CT) scans, retinal images, ultrasound imaging, and magnetic resonance imaging (MRI), as shown in Figure 1.1.

Several signal processing and data scientists have widely explored these modalities to develop automated screening tools. The core idea is to detect the presence of any visible symptoms of the underlying disease. It includes localization of normal and abnormal features, their segmentation, and eventually disease prediction. Such tools can be a tremendous help for medical professionals all over the world. In particular,



Figure 1.1: *Illustration of some medical imaging modalities: X-ray, CT, fundus, ultrasound, MRI from left to right. [Source : [www.wikipedia.com](http://www.wikipedia.com)]*

these can be boons for developing countries, with a huge population and disproportionate medical facilities. We can train non-medical professionals to use these tools for community-level testing. It will ease the burden on medicos and will be a definite help in improving the healthcare system.

The design of image-based automated diagnostic systems combine the techniques of image processing, computer vision and artificial intelligence. Recent improvements in the quality of image acquisition, high-speed data transfer, enormous data storage capacity, and computationally efficient processors are some factors that have collectively helped in such reliable automation. If programmed to detect the early symptoms of disease, they can help mitigate the ill effects to a large extent. Moreover, in cases of novel contagious diseases, these tools can quickly help filter out the positive cases to control the spread of infections.

For the past many years, medical images are being analysed using conventional image processing techniques. Researchers developed pipeline based algorithms to study various normal and abnormal features present in these images [6], [8], [10], [12], [18], [29], [30], [63], [79], [54], [80] etc. These methods commonly include template matching, filtering, image gradients, morphological transforms, edge detection etc. With the rising popularity of machine learning, these methods evolved into handcrafted feature extraction [13], [24], [32] etc. and then prediction (classification). Recently, the introduction of deep learning to diagnostics has made the process fully automatic [1], [86], etc. Here, convolutional layers learn to extract the high-level features for classification.

## 1.2 Diabetic Retinopathy

Diabetes Mellitus (DM), commonly termed diabetes, is a chronic disease. DM is characterized by hyperglycemia, a result of persistently uncontrolled blood sugar caused due to poor insulin management by the body [7]. As per WHO, about 422 million of the world's population is suffering from one or another form of diabetes (Type-I, II, or gestational). A large ratio of this figure belongs to the developing countries [27]. DM is a matter of huge concern as it affects the blood circulatory system of the body,

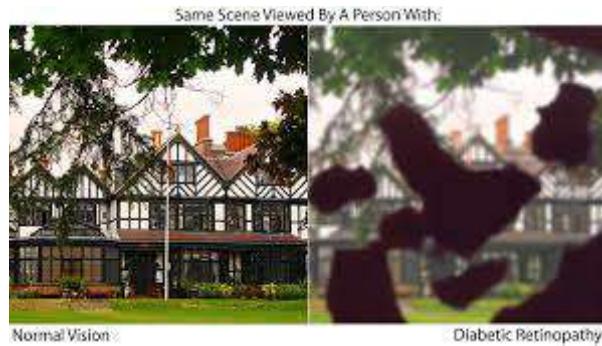


Figure 1.2: *Simulation result of Normal vision versus DR affected vision. The person with DR has a blurred view with floating patches.* [Source-<http://www.efei.com/diabetic-eye-disease>]

which eventually starts damaging other organs like the eyes, heart, kidneys, etc.

Diabetic Retinopathy (DR) is an eye complication associated with diabetes, in which the blood vessels present in the retinal layer get affected. A person having DM for more than 20 years will likely have DR [64]. In India, we have over 76 million of the population suffering from diabetes, about 18% have DR [27]. In the early stages, the DR is asymptomatic. It is recognizable only in the later stages when the patient starts observing blurry vision or floating spots in the eye. Figure 1.2 depicts a simulated DR-affected vision. Such advanced stages are difficult to treat and can lead into permanent vision loss [4]. Thus, an early diagnosis of DR is crucial.

### 1.2.1 Clinical Features

The retina is the innermost lining of the eyeball, which is made up of light-sensitive tissues. A healthy retina has features like an optic disc (OD), blood vessels, macula, fovea, etc. Figure 1.3 (a) shows a healthy retina and its features. DR progresses with the occurrence of various abnormalities in the retinal layer. It commonly includes microaneurysms, intra-retinal hemorrhages, vitreous hemorrhages, exudates, venous beadings, intra-retinal microvascular abnormality (IRMA), neovascularisation, etc. The fundus image can capture these clinical features in 2-dimension and facilitate us to analyze them. Here, we discuss some of the common features, briefly,

- **Red Lesions: Microaneurysms and Hemorrhages**

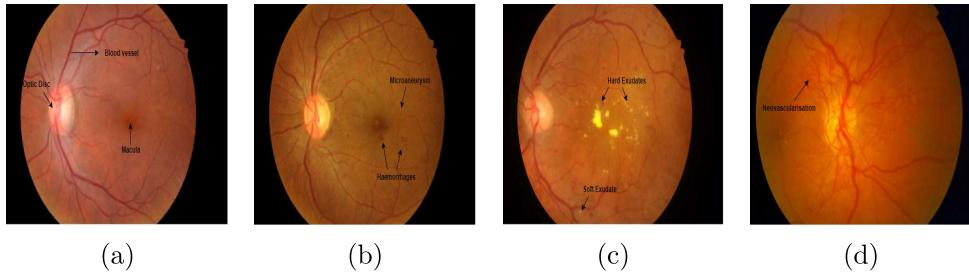


Figure 1.3: *Illustration of normal and abnormal features in retina : (a) Healthy retina with optic disc, blood vessels, and macula; (b) Retina with microaneurysms and hemorrhages (red lesions), (c) Retina with hard and soft exudates (bright lesions), (d) Retina with neovascularisation.*

The red lesions which include, microaneurysms (MAs) and hemorrhages (HEMs) are usually the early symptoms of DR [64], [86]. MAs appear as sharp red dots covering just a few pixels whereas, HEMs are comparatively more significant red patches caused due to leakage of blood in the retinal layer [54]. Red lesions are also referred to as dark lesions. Figure 1.3 (b) show an example of the MAs and HEMs on the retina.

- **Bright Lesions: Exudates**

The bright lesions include hard exudates (HEs) and soft exudates (SEs). The reason behind their occurrence is the leakage of lipids, proteins, etc., in the retinal layer. HEs are dark yellow with sharply defined boundaries, whereas SEs are light yellow/white with a cloudy appearance [54]. HEs and SEs on the retina are shown in Figure 1.3 (c).

- **Neovascularisation**

Neovascularisation occurs in the later stages of DR when the blood vessels become fragile. It is the abnormal growth of new, irregularly shaped, fragile vessels out of the original vessels [51]. A typical example of neovascularisation in the retina is shown in Figure 1.3 (d).

The presence of any of these visible abnormalities in the fundus image is a sign of DR. Generally, for early detection, experts look for the red lesions [64].

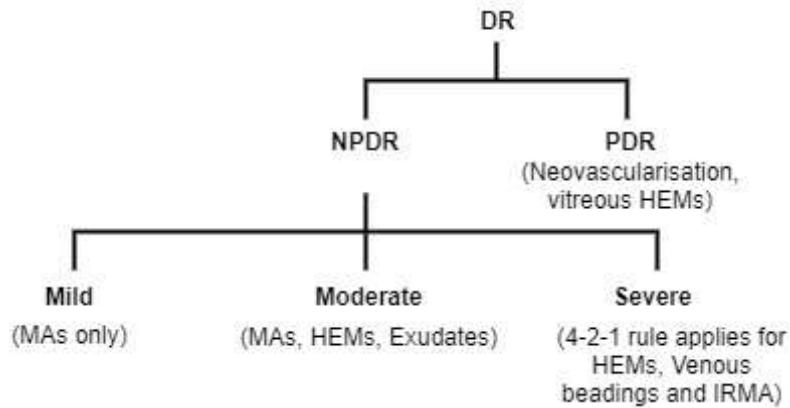


Figure 1.4: *Illustration of multiple stages of DR. The chart mentions the associated visible clinical features at each stage. [Source-Author's own]*

### 1.2.2 Stages of Diabetic Retinopathy

Broadly, DR progresses in two stages: Non-Proliferative DR (NPDR) and Proliferative DR (PDR). It starts with NPDR, which is further classified into mild, moderate and severe stages [51]. Mild NPDR is characterized by the appearance of a few MAs, which progresses towards the moderate stage with the appearance of more MAs, intra-retinal HEMs, and sometimes bright lesions. The stage when more than 20 intra-retinal HEMs appear in each of the four quadrants or venous beadings in two quadrants or IRMA in one quadrant (4-2-1 rule) is considered the severe NPDR [21]. Severe NPDR further evolves into PDR, which is characterized by neovascularisation or the appearance of vitreous hemorrhages [21]. Figure 1.4 illustrates a chart presenting the stages of DR and the corresponding clinical features.

### 1.2.3 Retinal Imaging

Ocular manifestations can be alarming signals about various retinal diseases like, DR, Glaucoma, Age-related Macular Degeneration (AMD), etc. Moreover, it can be the sign of various other systemic diseases such as hypertension, diabetes etc [3]. Today we have many high-end cameras to capture and project the 3D retinal layer (i.e., the fundus) into the 2D retinal image.

Fundoscopy is a non-invasive way to analyze the retinal layer. It lets the ophthal-

mologists look into the fundus of the eye feasibly. A fundus image can capture normal (OD, blood vessels, macula, fovea, etc.) as well as abnormal features (bright and dark lesions, fragile vessels, venous beadings, drusens, etc.) lying on the retina. The commonly preferred modalities for the examination and photography of the retinal fundus in DR screening are as follows,

- Fundus photography (red-free): it captures the images with intensities lying in a specific waveband [42].
- Color fundus photography: here, the image consists of intensities belonging to R, G, and B wavebands [42].
- Fluorescein angiography and Indocyanine angiography: here, the projected image intensities represent the emitted photons from the dye injected into the subject's circulation [42].

This work uses color fundus images as different channels may facilitate better information. Also, we use the green, mean gray channel, and all three channels for different algorithms.

### Digital Fundus photography

The term fundus means the inside of a hollow organ. Here, in our work, it refers to the inner lining of the eye i.e. the retina. As already mentioned, fundus images are the 2-D capture of the retinal layer, which enable ophthalmologists to look into the eye in a non-mydriatic way. A digital fundus camera has a specialized low power microscope, to analyze the retinal structures like optic disc, blood vessels, macula, any present abnormality, etc. Figure 1.5 (a) illustrates a typical table-top, non-mydriatic, digital fundus camera and figure 1.5 (b) presents an illustration of the view of retina when photographed using a digital fundus camera (non-mydriatic).

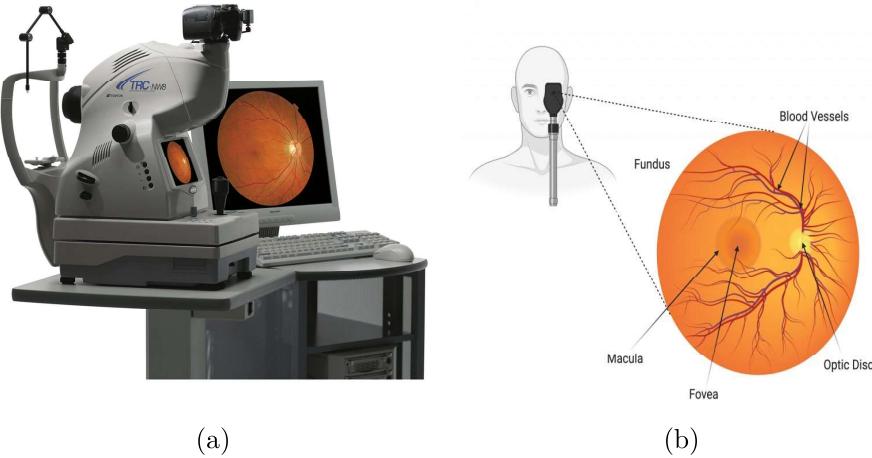


Figure 1.5: (a) A non mydriatic, digital fundus camera, Topcon TRC NW8 [Source-<https://www.digitaleyecenter.com>], (b) Illustration of 2-D projection of retina visible to the ophthalmologist [Source-<https://www.ucl.ac.uk/ioo/research/research-labs-and-groups/carr-lab/bestrophinopathies-resource-pages/eye/retina-and-retinal>]

### 1.3 Motivation

- Vessel extraction is crucial for the diagnosis of various retinal and systemic diseases such as diabetes, hypertension, etc.
- Precise segmentation of complete vessel map i.e., fine-to-coarse vessel extraction is essential to study the prognosis of DR.
- We can mask out the extracted vessel map to focus on the abnormalities appearing on the retinal layer. It majorly helps while detecting red lesions as the lesions and vessel pixels share a similar range of gray-scale intensities.
- Red lesions are the earliest symptoms of DR, which becomes irreversible in later stages. Thus, detection of these lesions helps in the prediction of the disease in early, curable stages.

## 1.4 Diabetic Retinopathy Screening

As discussed earlier, the DR is asymptomatic in its early stages. It requires regular monitoring of patients with diabetes. Without timely care and treatment, it may lead to permanent vision loss [20]. The commonly used practices for diagnosis of DR are comprehensive dilated eye examination, fluorescein angiography, and, Optical coherence tomography (OCT). These methods require trained medical staff to conduct the eye examination and make any decision. In developing countries, healthcare facilities are overburdened. Most of the population is ignorant as there are no early alarming symptoms to the patient, which can be understood and the high cost of the treatments. In such a scenario, the need for automated screening tools at community-level becomes inevitable.

Imaging-based, automated solutions can help the experts visualize and decide on the abnormality in much less time. Fundus images have provided a non-invasive mode to analyze the retinal layer. It captures both the normal and abnormal features present on the retina. Analysis of these features help in the diagnosis of not only the retinal diseases but also many other systemic diseases [3]. A 2-D fundus image is supposed to be a better modality as compared to other retinal images like FA, and OCTs [26]. The FAs require injection of dye inside the eye, and OCTs are captured using expensive machines. Also, both of these modalities need medical experts to capture the images. The fundus camera are relatively economic and do not need any invasion, thus make a preferred choice.

### 1.4.1 Fundus Image Dataset

In the proposed work, we have done experimentation with six different fundus image datasets available in the public domain. These are : DRIVE [11], STARE [8], CHASE\_DB-1 [13], HRF [48], IDRiD [77], and DDR [53]. Table 1.1 discusses some specifications of the above-mentioned datasets.

### 1.4.2 Unsupervised Vessel Segmentation

Segmentation of vessel map can help analyze the vessel morphology, which can further be used to study the progression of various diseases. Moreover, we can mask out the extracted vessel map to bring the focus to the other retinal abnormalities. Blood vessels are oriented, tubular structures of continuously varying width (mainly decreasing). While extracting vessel map, it is very likely to lose the boundary pixels, and fine vessel ends due to poor contrast with respect to the fundus background. Further, the arbitrary orientation, high tortuosity, and presence of abnormalities make the segmentation far more challenging.

Conventional image processing techniques are data independent. They have the potential to provide a reliable solution to a problem, even with fewer data. Researchers have widely explored these techniques for extracting vessel-like structures. Many groups assumed the cross-sectional intensity profile of vessel structures to be Gaussian in shape, thus applied matched filtering [6], [8], [9], [59]. Zana et al. [18], Mendonca et al. [22] etc. exploited the concepts of morphology to extract the retinal vessel map. Vessel modeling [29], active contours [30], [31] etc. are also explored. Multi-scaling [12], [61], [23], image matting-based methods [5], etc. are some more examples of classical vessel extraction methods.

In this thesis, we start with developing a rule-based retinal blood vessel segmentation algorithm, which is data-independent. We implement two multi-scale approaches, directional-wavelet transform (local application) and curvelet transform (global application), together in a novel manner for vessel enhancement. We also derive a generic Field-of-View (FoV) mask for extraction of Region-of-Interest (RoI). Further, we implement a morphological thickness-correction step to recover the boundary pixels of

Table 1.1: Fundus image datasets used in this work

S.No.	Dataset	No. of images (labeled)	Dimension (H x W)	FoV (in degree)
1	DRIVE [11]	40	584 x 565	45°
2	STARE [8]	20	605 x 700	35°
3	CHASE_DB1 [13]	28	960 x 999	30°
4	HRF [48]	45	2336 x 3504	45°
5	IDRiD [77]	103	2848 x 4288	50°
6	DDR [53]	757	NA	45°

vessels. This work has contributed significantly to the field of retinal image analysis by segmenting fine vessels and at the same time preserving the thickness of major vessels. Moreover, the algorithm is quite robust as it has performed consistently well on four different databases. Zero data dependency gives the suggested algorithm an edge over other state-of-the-art supervised methods.

### 1.4.3 Supervised Vessel Segmentation

In case of conventional image processing-based methods, though there is no requirement of prior knowledge about the ground truth, these methods are proved to be less generic. Recently, with the emerging computing and data storage facilities, supervised learning architectures have become quite popular. These methods can extract and learn deeply hidden information with the labeled data, which might have been over-looked while using conventional methods.

With the advent of machine learning, various supervised [13], [24], [32], etc., and unsupervised [45], [35] vessel extraction methods were proposed. The emergence of the deep learning has brought revolution in the field of automation and diagnostics. The Convolutional Neural Network (CNN) based methods [36], [37], [33], etc. has predicted quite promising retinal vessel maps. Generative adversarial networks (GAN's) based vessel extraction [40] tried to resolve the issue of data scarcity. Most of the state-of-the-art methods are based on Fully convolutional networks (FCN's). The most popular FCN in the field of medical image segmentation is U-net [71], [34], [74], [72], [76], etc.

The process of precise vessel extraction using fundus images is still a challenge due to spatially varying vessel-width and non-homogeneous retinal background. After developing a conventional image-processing-based vessel extraction, we move towards the supervised methods. We keep some of the previously explored classical techniques for pre-processing of fundus images. This work has targeted the aforementioned challenges with an adaptive multi-scale decomposition of input image and a novel characteristic patch-based deep network training. In order to enhance vessels of different widths, we use the observed field of view of the input image to estimate the most significant scales for Gabor decomposition. Enhanced vessel maps corresponding to real, imaginary, and

absolute coefficients at the estimated scales are linearly combined using a trainable  $1 \times 1$  convolutional layer of U-net. Moreover, the ‘characteristic patch-based training’ uses ‘random’ and ‘specific’ patches to learn the vessels in non-homogeneous retinal background. The proposed algorithm minimizes false negatives and extracts promising vessel maps in various challenging regions of the retina.

#### 1.4.4 Red Lesion Segmentation and DR Screening

In practice, most of the state-of-the-art DR detection algorithms focus on the image-classification entirely relying on machines. Professionals find such detection less communicative as there is no abnormality localization. Other algorithms which focus on locating or segmenting single or all kinds of lesions, are more complex, as there is a need to understand the minute differences in very similar structures. In the proposed work, we focus on detection of DR in any stage, which needs detection of initial symptoms which are common in all the stages of the disease. These symptoms are the red lesions. Eventually, our algorithm does not go into differentiation between MA and HEMs, which helps in avoiding unnecessary complexity. These lesions can be one pixel to several pixels wide, i.e. have no fixed size; may have poor contrast; and can be present anywhere on the retina. These are some of the factors which make their segmentation quite challenging.

DR-specific lesion detection using fundus images started with classical image enhancements methods. Researchers targeted abnormalities and then the pixel-wise classification is done for their detection. Various classical methods include, study of cross-sectional profile [78], watershed transform [63], curvelet transform [54], adaptive template matching [81] etc. Niemeijer et al. [67] used the k-NN classifier for red lesion detection. State-of-the-art methods are mostly CNN based. They include, [66], [68], [86], [70], [65], etc. For DR detection, the existing algorithms are mostly deep learning-based which have done global image-classification or gradation of images [84], [85], etc. A few of these approaches are based on abnormality localisation or segmentation ([86], [87], [88]), which are supposed to be more communicative and reliable, from the point of view of disease diagnosis.

In this work, we approach the DR screening by locating and precisely segmenting the DR-specific red lesions, which include MAs and HEMs. Here, we train a U-net architecture using ‘characteristic patches’ for segmentation. Moreover, we combine five intensity-based handcrafted features to the U-net extracted deep features for further improvement in the segmentation performance. As a pre-processing step, we inpaint the extracted vessel map before the patch-extraction, to bring the focus of the network to the vessel-free fundus background. Further, we use the presence of these red lesions for screening of DR.

Finally, for DR screening, we classify the input fundus images into two classes: No DR or DR. To infer this prediction from the segmented binary lesion map, we consider the mean area of lesions, denoted by  $A_{lesion}$ , which is evaluated morphologically. As the red lesion can be one to several pixels wide, we consider the non-zero value of this area parameter to be a DR predictor. Only zero value of  $A_{lesion}$  will mean ‘No DR’. This work has the potential to serve as a preliminary screening of DR, which can detect DR in any stage, including the early difficult ones.

## 1.5 Contribution of the Thesis

The main contributions of this thesis are as follows:

- This work presents an image-segmentation-based early DR screening.
- Analysis of 2-D retinal imaging modality (fundus images) is done.
- A classical multi-scale, pre-processing of fundus images is done, to enhance the fine-to-coarse retinal blood vessel map.
- A novel characteristic patch-based training of the deep model is done, to learn the structure of the vessel in various challenging fundus backgrounds.
- Segmentation of retinal blood vessels and DR-specific red lesions for detection of DR.

## 1.6 Organization of the Thesis

We organize this thesis into five chapters. The summary of the work presented in each chapter is briefly outlined as follows,

### **Chapter 1:**

This chapter discusses the importance of medical image analysis in the field of diagnostics and introduces the disease Diabetic Retinopathy. It includes the discussion of used imaging modality, the reported clinical features, and the stages in which the disease progresses. Moreover, a literature review of the related work done for vessel extraction, red lesion segmentation, and DR diagnosis is also presented. We also discuss the motivation and the contribution of this thesis.

### **Chapter 2:**

In this chapter, we have done a rule-based, unsupervised vessel extraction using fundus images. It uses conventional image processing techniques like continuous wavelet transform, discrete curvelet transform, morphological operations, etc., for image segmentation. Being data-independent, this method has the potential to provide a reliable solution for retinal blood vessel segmentation.

### **Chapter 3:**

In this chapter, we adopt the supervised way to improve the outcomes of Chapter 2. We use the previously observed wavelet enhanced vessel maps as input to a deep-learning model. We progress by studying the results of feeding three fixed scales as input to the U-net model (proposed supervised algorithm-1), to three scales along with texture suppressed maps (proposed supervised algorithm-2) to a final adaptive, characteristic patch-based training algorithm for blood vessel segmentation.

### **Chapter 4:**

In this chapter, we have done an early DR screening by red lesion segmentation. In this method, first, we remove the extracted blood vessels from the fundus, then focus on the red lesions, which include microaneurysms and hemorrhages. We use U-net extracted deep features along with five handcrafted intensity-based features to predict the lesion probability map. Further, we use the presence of segmented lesions

as deciding parameter for DR screening.

**Chapter 5:**

Finally, the conclusion and contributions of the presented work are discussed in this chapter. Moreover, we discuss the possible research directions in the future.