Decision support system for retinal health with digital fundus images

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

SINGAPORE

**DECISION SUPPORT SYSTEM FOR RETINAL HEALTH
WITH DIGITAL FUNDUS IMAGES**

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SCHOOL OF MECHANICAL AND AEROSPACE ENGINEERING

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**DECISION SUPPORT SYSTEM FOR RETINAL HEALTH
WITH DIGITAL FUNDUS IMAGES**

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Abstract

Background: Many health-related problems arise with aging. One of the diseases that are prevalent among the elderly is the loss of sight. Various eye diseases namely age-related macular degeneration, diabetic retinopathy, and glaucoma are the prime causes of vision loss as people grow old. Nevertheless, early detection of such eye diseases can impede the progression of this problem. Therefore, the elderly is encouraged to attend regular eye checkups for early detection of eye diseases. However, it is time-consuming and laborious to conduct a mass eye screening session frequently. This thesis proposes a retinal screening system to automatically differentiate normal image from abnormal (AMD, DR, and glaucoma) fundus images.

Methods: To achieve these, two methods will be used. The first method uses the combination of pyramid histogram of oriented gradients (PHOG) and speeded up robust features (SURF) technique. Then, the extracted data are subjected to adaptive synthetic sampling to balance the number of data in the two classes. Subsequently, the canonical correlation analysis approach to fuse the highly-correlated features extracted from the two (PHOG and SURF) descriptors was used.

The second method applies pyramid histogram of visual words (PHOW) for the detection of retinal health with digital fundus images using Fisher vector and visual vocabularies. The algorithm can discriminate four classes. As the aim is to get the best performance with the least number of features, the second method outperforms the first method.

Results: An average accuracy, sensitivity, and specificity of 96.21%, 95.00%, and 97.42% respectively is obtained using the first method for the classification of normal and abnormal classes using ten-fold cross validation. An average accuracy, sensitivity, and specificity of 96.79%, 96.73%, and 96.96% respectively is obtained using the

second method for the classification of normal, AMD, DR and glaucoma classes using ten-fold cross validation.

This work has high potential in the diagnosis of normal eye during the mass eye screening session or in polyclinics quickly and reliably. Hence, the patients having abnormal eye can be sent to the main hospitals which will reduce the workload for the ophthalmologists.

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Nomenclatures

$\mathbb{R}$	Real numbers
S	Covariance matrix
X^*	Affinely extended matrix
W_x	Eigenvectors
Λ^2	Diagonal matrix of eigenvalues/squares of canonical correlations
d	Number of non-zero eigenvalues
Z	Canonical correlation discriminant features
L	Gaussian blurred image
m	Magnitude
θ	Orientation

Chapter One

Introduction

According to the world health organization (WHO) report on visual impairment in 2010, it is estimated that globally, 246 million people suffer from low vision and 39 million people are blind (World Health Organization, 2012). Also, 65% of the people visually impaired and 82% of all blind are aged 50 years and older. From a study conducted between 2004 to 2006, the Singapore Malay Eye Study (SiMES-1) found that from a group of 3,280 randomly selected Malay adults, 4.6% of the participants have glaucoma, 12.9% have diabetic retinopathy (DR), 5.6% have age-related macular degeneration (AMD) and 45.7% have unilateral cataract (Rosman et al., 2012). It is noted that the prevalence of visual impairment is similar among the various ethnic groups in Singapore (Wong et al., 2012). Cataract is the leading cause of blindness and visual impairment, contributing a high percentage of 33%, while AMD, DR, and glaucoma contributing to around 1% globally. These four eye diseases are listed by the WHO as priority eye diseases which can be managed and prevent the loss of vision if detected at an early stage (World Health Organization, 2012).

These eye diseases (AMD, cataract, DR, and glaucoma) are prevalent among the elderly (Katibeh et al., 2014). Moreover, according to the WHO, the population are aging. The statistics of people age 60 years and older will increase from 900 million to 2 billion between 2015 and 2050 (World Health Organization, 2016). Furthermore, older people are more prone to diseases and their health deteriorates at a faster pace (Novak, 2012). This is a big worry for the aged people in the society. The visual impairment is a burden not only to the individual but also to his family and his caregiver (Bambara et al., 2009). Therefore, it is necessary for the elderly to take measures such

as attending an annual eye screening session for early detection of the various eye diseases. Then, the progression of the various eye diseases (AMD, cataract, DR, and glaucoma) can be moderated or controlled.

1.1 The Human Eye

The human eye is a system that contains a complex system that takes in light rays and converting to electrical signals that travels through the nerves and guides our interaction with the surroundings (Remington, 2012). The electrical signals carries visual information to the brain, the lens focuses on near and distant objects and the iris restricts the amount of light entering the eye (Remington, 2012).

The orbit, is a bony structure that housed the eyeballs, the extraocular muscle, connective tissues, the nerves and blood vessels, along with the lacrimal secretory system that drains and produces tears (Remington, 2012).

The sclera is the tough white layer that covers the eyeball. The cornea, on the other hand is the clear and curved protective front covering of the eye. Light traveling through the pupil will pass through the cornea and using refraction of the lens, which can be changed through the contraction of the ciliary muscles, enables near objects to be focused light onto the retina (Remington, 2012).

The iris is a colored circular area which dilates or constricts the pupil to controls the amount of light, like the aperture of a camera lens (Remington, 2012).

The retina is the part where light is converted into signals by photoreceptors and the contains nutrients-providing blood vessels. There are two types of photoreceptors: cones and rods. Cones are less sensitive in dim lighting and in bright condition the ability to recognize detail and colour. Rods are sensitive to dim lighting; however, objects appear in gray and less details (Remington, 2012).

The macula appears as a darkened region on the retina, it contains the highest concentration of cones, estimate to be around 199,000 to 300,000 cones per square millimeter. In the peripheral area of the retina, the ratio of rods to ganglion cells (Remington, 2012).

At the back of the eye, there is the optic disk where optic nerves bundles together and exit the eye. There are no photoreceptors in the optic disk, resulting in a physiological blind spot (Remington, 2012).

The anterior segment consists of the anterior and posterior chambers, containing aqueous humor which provide nutrients and oxygen to the cornea and lens. It is produced in the ciliary body, into the posterior chamber and passes between the iris and lens through the pupil into the anterior chamber, where it circulates by convection currents generated by the cooler cornea and the warmer iris and out through the trabecular meshwork through the tissues and lining into the Schlemm's canal at periphery of the chamber. An angle is form at the periphery of the chamber (Remington, 2012).

The posterior segment or vitreous chamber contains a gel like substance, known as vitreous gel, which provide support to hold the retina in place next to the blood supply for the outer retina or choroid. The vitreous contain metabolites for the retina and lens and due to it viscoelastic properties, it is able to protect the fragile retina tissues by absorbing shock during rapid movement of the eye and strenuous physical activities (Remington, 2012). Figure 1.1 shows a typical anatomy of an eye.

Figure 1.1: Anatomy of the human eye.

1.2 Age-Related Macular Degeneration (AMD)

The AMD is a common cause of vision loss in people over the age of 50 years. The macula in the retina is damaged and thus, the central vision is blurred. Over time, the damage grows larger and blank spots might appear in the central vision. The loss of central vision interferes with daily living activities such as driving and the ability to see faces clearly (Mitchell & Bradley, 2006; Taylor et al., 2016).

Moreover, the damages caused by AMD are irreversible. Generally, there are two types of AMD: dry AMD and wet AMD (Mitchell & Bradley, 2006).

1.2.1 Dry AMD

Dry AMD is caused by the development of yellowish deposits called drusens under the macula (Lim & Laude, 2007). This causes the narrowing and drying of the macula, leading to the degeneration of macula. Hence, no leakage of blood is involved in the dry

form of AMD. Only drusens and pigmentary abnormalities are present in the macula (Bird et al., 1995).

The gradual loss of central vision is painless across many years. Central blind spots usually occur in the later stage of the disease and can become severe. The symptoms usually occur in both eyes (Mitchell & Bradley, 2006).

1.2.2 Wet AMD

The development of wet AMD is a process called choroidal neovascularization. New abnormal blood vessels develop under the retina. These vessels are extremely thin and thus, break easily, causing the vessels to bleed under the macular. The leakage might spread into the vitreous cavity (gel-like structure in front of retina) and cause a scar at the macula (Mitchell & Bradley, 2006).

Also, the wet AMD is considered as an advanced form of AMD. The rapid vision loss over days to weeks is typical of the wet form of AMD. The patients may become legally blind in the affected eye, if left untreated. It is different from dry form of AMD as the wet form usually affects one eye at a time (Mitchell & Bradley, 2006).

Figure 1.2 compares a typical graphical representation of a normal, dry AMD, and wet AMD fundus images.

Figure 1.2: Typical fundus image of (a) Normal (b) Dry AMD (c) Wet AMD.

1.3 Cataract

Cataract refers to the clouding of lens in the eyes. The lens is a part of eye which enables us to focus on images on the retina. In a normal eye, light can pass through the transparent lens to the retina. However, in a cataract eye, the lens is clouded, resulting in a blurry image. The formation of cataracts is presumed to be caused by a number of factors, including damage caused by oxidation, an imbalance in fluid and ion, protein modification and metabolic disruption. Ion and fluid imbalance will result in water to accumulate, causing the lens fiber to swell and diminishes transparency and can form vacuoles increasing light scatter by disrupting the arrangement of fibers. In addition, free radical accumulation oxidative damage and ultraviolet ray can affect cellular function, damage DNA of the lens, causing protein modification and crystalline aggregations from ultraviolet ray and oxidative damage due to accumulation of free radical. Light scattering opacities formed with time due to an accumulation of aggregates (Remington, 2012).

Cataracts are named according to the cause or location and graded base on severity.

1.3.1 Diabetic Cataract

Diabetic cataract can develop rapidly from elevated glucose levels. Sorbitol concentration increases as the rate of excess glucose is converted to sorbitol is faster than the rate of sorbitol being converted to fructose. This results in the swelling of the fibre and the transparency of the lens is lost, as sorbitol is unable to pass through the fibre membrane readily. Might eventually rupture the fibres (Remington, 2012).

1.3.2 Age-related Cortical Cataract

Increased incidence of cortical cataract is correlated with high lifetime exposure to ultraviolet rays, resulting in increased permeability of the membrane and the homeostatic concentration cannot be maintained by the ion transporters, pumps and

exchangers (Delamere & Tamiya, 2009; Remington, 2012). The cataracts generally occur at the equatorial region (Remington, 2012).

1.3.3 Age-related Nuclear Cataract

A decline in glutathione makes the fibres vulnerable to oxidative damage resulting in age-related nuclear cataract. The oxidative modification of proteins increases significantly after the age of 50. The colour can be brown or yellow (Remington, 2012).

1.3.4 Posterior Sub-Capsular Cataract

Epithelial-like cells moved from the equatorial region and accumulates at the posterior pole forming an opacity in the posterior sub-capsular region. Radiation damage may be a cause, as cancer patients develop posterior sub-capsular and/or cortical cataracts go through radiation therapy. Sutural congenital cataracts caused by the swelling of the basal ends of the fibres also occurs at this location (Remington, 2012).

1.3.5 Steroid-induced Cataract

Steroid use appears to be a factor in steroid-induced cataract, which can affect children at a faster rate than adults, different levels of susceptibility in individuals. Undifferentiated epithelial cells appear to form the opacity at the interface of the posterior cortex and capsule. Cellular process can be affected if the production of growth factors in the aqueous, the location in the capsule and concentration is changed by steroid use (Remington, 2012).

Cataract can be removed, and an intraocular lens is inserted into the lens capsule to replace the missing lens, when patients are unable to perform the usual activities of daily living. Figure 1.3 shows a typical image of an eye with and without nuclear cataract (Remington, 2012).

Figure 1.3: Typical optical image of (a) Normal eye (b) Eye with nuclear cataract.

1.4 Diabetic Retinopathy (DR)

DR is a complication of diabetes, caused as a result of damaged capillaries in the retina due to chronic high blood sugar. The damaged capillaries leak fluid or haemorrhage easily (ETDRSG, 1991). At an advanced stage, neovascularization develops on the surface of the retina causing scarring and cell loss (Friedlander, 2007).

There are two main stages of DR: non-proliferative DR (NPDR) and proliferative DR (PDR). According to a paper by the Early Treatment Diabetic Retinopathy Study Research Group (ETDRSG), NPDR can be further graded into mild, moderate and severe. Diabetic macular edema (DME) more likely to occur in the advanced stage of DR (ETDRSG, 1991; Faust et al., 2012).

1.4.1 Non-Proliferative DR (NPDR)

The NPDR is characterized by an increase in the abnormalities of the structure of the capillaries, micro-aneurysms, haemorrhages, exudates, macular ischemia, and edema (Neely et al., 1998). Also, there are little or no symptoms during the early stage of non-proliferative DR. Therefore, it is a good practice for diabetic patients to go for annual eye checkups.

1.4.2 Proliferative DR (PDR)

As the NPDR stage worsens, it develops into PDR, the advanced stage of DR leading to the growth of new blood vessels which are very near to the retina and/or optic disc. The new blood vessels might result in a retinal detachment which causes an sudden loss of vision (ETDRSRG, 1991; Hudson, 2008).

Figure 1.4 is a graphical representation of a normal, non-proliferative DR, and proliferative DR fundus image.

Figure 1.4: Typical fundus image of (a) Normal (b) Non-proliferative (c) Proliferative.

1.5 Glaucoma

Glaucoma is characterized by an increase in relative intraocular pressure, caused by the accumulation of aqueous humor in the eye, leading to progressive optic nerve damage. As glaucoma progresses, it can lead to an irreversible loss of vision (Boyd & Mckinney, 2017). Therefore, it is highly recommended that, people especially the elderly to go for regular eye checkups.

There is two main type of glaucoma: primary open-angle glaucoma and angle-closure glaucoma (Boyd & Mckinney, 2017).

1.5.1 Primary Open-Angle Glaucoma (POAG)

The primary open-angle glaucoma is the most common form of glaucoma. It occurs when the aqueous humor drainage is inadequate, while the production is normal. This increases the intraocular pressure, due to the accumulation of fluid in the eye (Boyd & Mckinney, 2017).

1.5.2 Primary Angle-Closure Glaucoma (PACG)

Primary angle-closure glaucoma is the less common form of glaucoma. This form of glaucoma is also known as the narrow-angle glaucoma as the eye cannot drain extra fluid efficiently because the space between the iris and cornea is constricted (Boyd & Mckinney, 2017).

A typical normal and glaucomatous fundus images are shown in Figure 1.5.

Figure 1.5: Typical fundus image of (a) Normal (b) Glaucoma.

Table 1.1 summarizes the diagnostic methods used to diagnose the *four* eye diseases. It can be noted that AMD, DR, and glaucoma can be diagnosed by the manual inspection of fundus image (Abràmoff et al., 2010a; ETDRSRG, 1989). The fundus imaging is safe, inexpensive and accurately capture retinal abnormalities (Abràmoff et al., 2010a).

However, the diagnosis of cataract does not involve the use digital fundus image (see Table 1.1). Thus, only AMD, DR, and glaucoma will be discussed in the subsequent chapter.

In this chapter, the anatomy of the human eye, the various eye diseases (AMD, cataract, DR, and glaucoma), and the clinical diagnostic methods are briefly discussed. Cataract is not diagnosed using fundus images but can be detected using optical images. Thus, in this report eye diseases that can be detected using fundus image like AMD, DR and glaucoma are considered.

Table 1.1: Summary of diagnosis methods used to diagnose various eye diseases.

Eye Diseases	Methods
AMD	Funduscopy <i>Colour fundus photographs</i> Flourescein angiography Optical Coherence Tomography
Cataract	Funduscopy Slit-lamp examination
DR	Funduscopy <i>Colour fundus photographs</i> Flourescein angiography Optical Coherence Tomography
Glaucoma	Funduscopy <i>Optic disc fundus photographs</i> Visual field testing Measurement of central corneal thickness Intraocular Pressure Exclusion of other optic neuropathies

1.6 Objective and Scope

To develop an economical and effective decision support system to aid the diagnoses of the various eye diseases, it is important to experiment with different features and classification methodology.

The scope of this project it:

- 1) To use normal, AMD, DR and glaucoma as 2 classes by combining diseases images as one class and as 4 classes with each disease as individual class.
- 2) To come out with a system to help to screen for abnormal eye diseases and to reduce the workload of ophthalmologist in main hospital using conventional methods of classification.

1.7 Organization of the Thesis

The subsequent chapters of this thesis are organized as follows:

- The report starts with a review of the different methodologies done using fundus images. The Chapter Two, provides the motivation for fundus imaging, the types of databases used, the methods applied, and results obtained from the various studies done on AMD, DR, glaucoma and abnormal retinal are discussed.

- Chapter Three proposes a novel method for the classification of normal and abnormal (DR, AMD, and glaucoma) fundus images using pyramid histogram of oriented gradients (PHOG) and speeded up robust features (SURF) techniques.
- A novel algorithm using the pyramid histogram of visual words (PHOW) and Fisher vectors is proposed for the classification of fundus images into their respective eye conditions (normal, AMD, DR, and glaucoma) in Chapter Four.
- A discussion on the proposed two methods is provided Chapter Five.
- The thesis concludes in Chapter Six with conclusion and future work of this work.

Chapter Two

Literature Review

Fundus image processing is a major research area over the past few decades, with the objective of providing computational tools to assist quantification, visualization of pathology and anatomical structures (Abràmoff et al., 2010a). Fundus image analysis is a noninvasive technique to diagnose the quality of an eye and its abnormalities. This is because the state-of-art image processing algorithms can provide better visualization of features concealed in the fundus images. Also, the advantages of inexpensive ophthalmic imaging devices coupled with the advanced image processing techniques have encouraged researchers to develop an automated CAD system for the detection of eye abnormalities.

A typical CAD system consists of a few processes: (i) pre-processing, (ii) feature extraction, (iii) feature selection, and (iv) classification.

The aim of the pre-processing step is to ensure that all fundus images are standardized and are enhanced. Furthermore, this step removes unwanted noise present in the fundus images. Then the enhanced images are subjected to feature extraction process. The morphological features, textural features, nonlinear features, and wavelet-based features are commonly extracted from the fundus images. These features can capture subtle pixel variations in the images and hence, pick up significant features. Usually, the feature extractor extracts too many features therefore, a feature selection approach is needed. In this process, the different feature selection techniques are employed to select only highly relevant and correlated features for classification. Finally, the selected features will be inputted into a classifier algorithm. Figure 2.1 shows a typical block diagram of a proposed CAD algorithm.

Hence, in this chapter, a review of the extensive works done on CAD systems to detect AMD, DR, and glaucoma are presented. Tables 2.1 to 2.4 is a summary of selected studies on the development of CAD system to detect AMD, DR, glaucoma, and abnormal (DR, AMD and glaucoma) eye diseases respectively.

Figure 2.1: A typical block diagram of a proposed CAD algorithm.

2.1 Computer Aided Diagnosis System for AMD

An automated AMD detection system detects AMD commonly using fundus images. Region growing technique (Köse et al., 2008) and statistical approach (Köse et al., 2010) are employed to segment and identify the area of degeneration in the fundus images.

It can be noted from Table 2.1 that, most of the researchers obtained their fundus images from open source databases such as the automated retinal image analyzer (ARIA) and structured analysis of the retina (STARE). Also, nonlinear feature extraction technique (Hijazi et al., 2014; Mookiah et al., 2014a, 2015a), wavelet-based technique (Acharya et al., 2016b; Hijazi et al., 2014; Mookiah et al., 2014a, 2014b), statistical methods (Hijazi et al., 2014; Mookiah et al., 2014b), and textural features (Mookiah et al., 2015b) are the common feature extraction approaches employed to capture subtle pixel variations present in the fundus images.

Furthermore, AMD risk index is formulated in few studies (Acharya et al., 2016b; Mookiah et al., 2014b). The AMD risk index can differentiate normal and AMD fundus images with just a single value developed using clinically significant features.

Recently, Acharya et al. (Acharya et al., 2017) extended this work to three-class AMD problem (normal, dry AMD, and wet AMD). However, the number of wet AMD fundus images used is too few. Hence, to balance the number of images in each class, they have performed adaptive synthetic sampling (AdaSyn) approach.

Table 2.1: Summary of studies for automated screening system for normal and AMD classes using fundus images.

Author (Year)	Databases	Number of Images	Methods	Performance
Normal and AMD				
(Köse et al., 2008)	KTU ¹	Normal: 30 AMD: 30	Sobel filter, region growing	(Area) $A_{CC} = > 90.00\%$
(Köse et al., 2010)	KTU	Normal: 40 AMD: 40	Statistical segmentation	(Small area of degeneration) $A_{CC} = 89.59\%$
				(Medium area of degeneration) $A_{CC} = 92.69\%$
				(Large area of degeneration) $A_{CC} = 93.03\%$
(Agurto et al., 2011)	RIST ² UTHSCSA ³	(RIST) Normal: 64 AMD: 247 (UTHSCSA) Normal: 116 AMD: 271	Features: AM-FM	PLS classifier $AUC = 0.84$ $S_{EN} = 0.94$ $S_{PEC} = 0.50$
(Hijazi et al., 2012)	ARIA	Normal: 60 AMD: 101	Features: Spatial histograms, hierarchical decomposition	SVM classifier: (Spatial histogram) $A_{CC} = 74.00\%$ $S_{EN} = 100.00\%$ $S_{PEC} = 100.00\%$ (Hierarchical decomposition) $A_{CC} = 100.00\%$ $S_{EN} = 100.00\%$ $S_{PEC} = 100.00\%$

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³ University of Texas Health Science Center

Author (Year)	Databases	Number of Images	Methods	Performance
(Zheng et al., 2012)	ARIA STARE ⁴	(ARIA) Normal: 60 AMD: 101 (STARE) Normal: 38 AMD: 59	Features: WFSG mining algorithm	SVM classifier: $A_{CC} = 99.60\%$ $S_{EN} = 99.40\%$ $S_{PEC} = 100.00\%$
(Mookiah et al., 2014a)	ARIA KMC ⁵ STARE	(ARIA) Normal: 101 AMD: 60 (KMC) Normal: 270 AMD: 270 (STARE) Normal: 36 AMD: 47	Features: Fractal dimension, Gabor wavelet, entropy, HOS, radon transform t-test, KLD, CBBB, ROC- based, Wilcoxon ranking	SVM classifier: (ARIA) t-test ranking: $A_{CC} = 95.07\%$ $S_{EN} = 96.09\%$ $S_{PEC} = 93.33\%$ (KMC) CBBB ranking: $A_{CC} = 90.19\%$ $S_{EN} = 88.89\%$ $S_{PEC} = 91.48\%$ (STARE) KLD ranking: $A_{CC} = 95.00\%$ $S_{EN} = 96.00\%$ $S_{PEC} = 93.33\%$
(Mookiah et al., 2014b)	KMC	Normal: 270 AMD: 270	Features: DWT, statistical energy, entropy Gini index, t-test, KLD, CBBB, ROC-based, Wilcoxon ranking, AMD risk index	SVM classifier: $A_{CC} = 93.70\%$ $S_{EN} = 91.11\%$ $S_{PEC} = 96.30\%$
(Hijazi et al., 2014)	ARIA STARE	(ARIA) Normal: 60 AMD: 101 (STARE) Normal: 38 AMD: 64	Features: Pixel color information features, Color histogram features, Correlation, energy, entropy, DWT features	Tree classifier: $A_{CC} = 99.90\%$ $S_{EN} = 99.00\%$ $S_{PEC} = 100.00\%$

⁴ Structured Analysis of the Retina

⁵ Kasturba Medical College

Author (Year)	Databases	Number of Images	Methods	Performance
(Mookiah et al., 2015a)	ARIA KMC STARE	(ARIA) Normal: 101 AMD: 60	Features: Radon transform, EMD, HOS, nonlinear, entropy	SVM classifier: (ARIA) $A_{CC} = 85.09\%$
		(KMC) Normal: 270 AMD: 270	LSDA, MRMR, KLD, CBBB	(KMC) $A_{CC} = 91.67\%$
		(STARE) Normal: 36 AMD: 47		(STARE) $A_{CC} = 100.00\%$
(Mookiah et al., 2015b)	ARIA KMC STARE	(ARIA) Normal: 101 AMD: 60	Features: Local configuration patterns	SVM classifier: (ARIA) $A_{CC} = 91.36\%$ $S_{EN} = 92.18\%$ $S_{PEC} = 90.00\%$
		(KMC) Normal: 270 AMD: 270	t-test	(KMC) $A_{CC} = 93.52\%$ $S_{EN} = 91.11\%$ $S_{PEC} = 95.93\%$
		(STARE) Normal: 36 AMD: 47		(STARE) $A_{CC} = 97.78\%$ $S_{EN} = 98.0\%$ $S_{PEC} = 97.50\%$
(Acharya et al., 2016b)	ARIA KMC STARE	(ARIA) Normal: 101 AMD: 60	Features: DWT, radon transform	(ARIA) SVM classifier: $A_{CC} = 96.89\%$ $S_{EN} = 100.00\%$ $S_{PEC} = 91.67\%$
		(KMC) Normal: 404 AMD: 381	LSDA, t-test, AMD index	(KMC) DT classifier: $A_{CC} = 99.49\%$ $S_{EN} = 99.21\%$ $S_{PEC} = 99.75\%$
		(STARE) Normal: 36 AMD: 47		(STARE) SVM classifier: $A_{CC} = 100.00\%$ $S_{EN} = 100.00\%$ $S_{PEC} = 100.00\%$
Normal, Dry and Wet				
(Acharya et al., 2017)	KMC	Normal: 404 Dry AMD: 517 Wet AMD: 24	Features: PHOG, energy, entropy, nonlinear AdaSyn, ACO- GA, PSO, ANOVA	SVM classifier: ACO-GA: $A_{CC} = 83.83\%$ $S_{EN} = 82.65\%$ $S_{PEC} = 84.83\%$ PSO: $A_{CC} = 85.12\%$ $S_{EN} = 87.24\%$ $S_{PEC} = 80.09\%$

2.2 Computer Aided Diagnosis System for DR

The first work of an automated DR eye screening algorithm was developed in 1996 by Gardner et al. (Gardner et al., 1996). Subsequently, more researchers have developed the CAD system to diagnose DR with fundus images (see Table 2.2). Morphological methods (Acharya et al., 2009; Antal & Hajdu, 2012; Gardner et al., 1996; Lee et al., 2005; Mookiah et al., 2013; Nayak et al., 2008; Roychowdhury et al., 2014; Saleh & Eswaran, 2012; Usher et al., 2004; Yun et al., 2008), nonlinear features (Acharya et al., 2008; Mookiah et al., 2013), statistical techniques (Acharya et al., 2008), template matching (Abràmoff et al., 2010b), textural algorithms (Acharya et al., 2012; Mookiah et al., 2013), and wavelet-based transforms (Noronha et al., 2013) are used for the characterization of DR classes. Furthermore, Pratt et al. employed convolutional neural network to classify DR classes (Pratt et al., 2016).

Majority of the works have extracted the morphological features such as blood vessels, exudates, and hemorrhages to identify the fundus images. Typically, the presences of these morphological features are indicators of DR.

There are also two-class (normal and DR), three-class (normal, NPDR and PDR), four-class (normal, mild/moderate, moderate/severe and proliferative), and five-class (normal, mild, moderate, severe and proliferative) DR CAD systems proposed. Also, from the exhaustive list in Table 2.2, it can be noted that many CAD systems have been proposed to diagnose DR classes. It is because always patients with diabetes ultimately lead to DR and if detected early can save vision. Hence, this will help the clinicians in their diagnosis too.

Table 2.2: Summary of studies for automated screening system for normal and DR classes using fundus images.

Author (Year)	Databases	Number of Images	Methods	Performance
Normal and DR				
(Gardner et al., 1996)	-	Normal: 133 DR: 347	Features: Vessels, exudates, haemorrhages	NN classifier: $S_{EN} = 88.40\%$ $S_{PEC} = 83.40\%$
(Usher et al., 2004)	-	Normal: 399 DR: 874	Features: Lesions size, shape, hue, and intensity	NN classifier: $S_{EN} = 95.10\%$ $S_{PEC} = 46.30\%$
(Abràmoff et al., 2010b)	EyeCheck project	Normal: 15,977 DR: 793	Features: Pixels (EyeCheck)	kNN classifier $AUC = 0.839$
(Agurto et al., 2010)	MESSIDOR ⁶	Normal: 0 DR: 376	Features: AM-FM PCA, K-means, partial least squares	PLS classifier $AUC = 0.84$
(Antal & Hajdu, 2012)	ROC ⁷ MESSIDOR	(ROC) Normal: 23 DR: 77 (MESSIDOR) Normal: 540 DR: 660	Features: Micro-aneurysm Ensemble of preprocessing methods and candidate extractors	Ensemble: $AUC = 0.90 \pm 0.01$
(Noronha et al., 2013)	KMC	Normal: 120 DR: 120	Features: DWT Diabetic retinopathy risk index	SVM classifier: $A_{CC} = 99.17\%$ $S_{EN} = 99.17\%$ $S_{PEC} = 99.17\%$
(Ganesan et al., 2014)	KMC MESSIDOR	(KMC) Normal: 170 DR: 170 (MESSIDOR) Normal: 170 DR: 170	Features: Trace transform	PNN-GA classifier: (KMC) $A_{CC} = 99.41\%$ $S_{EN} = 99.41\%$ $S_{PEC} = 99.41\%$ (MESSIDOR) $A_{CC} = 100.00\%$ $S_{EN} = 100.00\%$ $S_{PEC} = 100.00\%$

⁶ Methods to evaluate segmentation and indexing techniques in the field of retinal ophthalmology (MESSIDOR)

⁷ Retinopathy Online Challenge

Author (Year)	Databases	Number of Images	Methods	Performance
Normal, Non-Proliferative and Proliferative				
(Nayak et al., 2008)	KMC	Normal: 49 Non-proliferative: 55 Proliferative: 36	Features: Blood vessels, exudates, texture	NN classifier: $A_{CC} = 93.00\%$ $S_{EN} = 90.00\%$ $S_{PEC} = 100.00\%$
(Mookiah et al., 2013)	KMC	Total: 156	Features: Area of blood vessels, exudates, bifurcation points, texture, entropies	PNN classifier $A_{CC} = 96.15\%$ $S_{EN} = 96.27\%$ $S_{PEC} = 96.08\%$
GA, PSO				
(Usman et al., 2013)	DRIVE STARE DIARETDB MESSIDOR	(DRIVE) Normal: 19 Neo Vasculature (OD): 0 Neo Vasculature (Others): 3 (STARE) Normal: 30 Neo Vasculature (OD): 3 Neo Vasculature (Others): 4 (DIARETDB) Normal: 5 Neo Vasculature (OD): 3 Neo Vasculature (Others): 5 (MESSIDOR) Normal: 397 Neo Vasculature (OD): 27 Neo Vasculature (Others): 18	Features: Vessel patterns	m-Medioids classifier: (DRIVE) $A_{CC} = 100.00\%$ (STARE) $A_{CC} = 97.53\%$ (DIARETDB) $A_{CC} = 97.75\%$ (MESSIDOR) $A_{CC} = 98.24\%$
Normal, Mild/Moderate, Moderate/Severe and Proliferative				
(Lee et al., 2005)	Vision Keepers	Total: 430	Features: Exudates, hemorrhages, micro-aneurysms, cotton wool spots	(430 images) $A_{CC} = 81.70\%$ (361 images) $A_{CC} = 83.50\%$
(Yun et al., 2008)	NUH ⁸	Normal: 29 Moderate: 38 Severe: 18 Proliferative: 39	Features: Area of blood vessel	NN classifier: $A_{CC} = 84.00\%$ $S_{EN} = 90.00\%$ $S_{PEC} = 100.00\%$
(Acharya et al., 2012)	MESSIDOR	Normal: 60 Non-proliferative: 40 Proliferate: 50 Macular Edema: 30	Features: Texture Integrated DR index	SVM classifier: $A_{CC} = 85.20\%$ $S_{EN} = 98.90\%$ $S_{PEC} = 89.50$

⁸ National University Hospital, Singapore

Author (Year)	Databases	Number of Images	Methods	Performance
(Saleh & Eswaran, 2012)	UMMC ⁹	Normal: 22 Mild: 36 Moderate: 28 Severe:12	Features: Haemorrhages, micro-aneurysms	Rule-based grading: (Microaneurysms) $S_{EN} = 84.31\%$ $S_{PEC} = 93.63\%$ (Haemorrhages) $S_{EN} = 87.53\%$ $S_{PEC} = 95.08\%$
(Roychowdhury et al., 2014)	DIARETDB1 MESSIDOR	DIARETDB1: 89 MESSIDOR: 1,200	Features: Area, pixel intensity, distance, Two-step hierarchical binary classification	GMM+KNN classifiers: $S_{EN} = 100.00\%$ $S_{PEC} = 53.16\%$ $AUC = 0.904$
(Abràmoff et al., 2016)	MESSIDOR-2	Total: 1,748	Features: Features vectors CNN-based detectors	RF-fusion classifiers: $S_{EN} = 96.80\%$ $S_{PEC} = 87.00\%$ $AUC = 0.980$
Normal, Mild, Moderate, Severe and Proliferative				
(Acharya et al., 2008)	NUH	Normal: 60 Mild: 60 Moderate: 60 Severe: 60 Proliferative: 60	Features: Higher order spectra	SVM classifier: $A_{CC} = 82.00\%$ $S_{EN} = 92.00\%$ $S_{PEC} = 88.00\%$
(Acharya et al., 2009)	NUH	Normal: 62 Mild: 73 Moderate: 65 Severe: 71 Proliferative: 60	Features: Vessel, exudates, hemorrhages, microaneurysms	SVM classifier: $A_{CC} = 85.90\%$ $S_{EN} = 82.00\%$ $S_{PEC} = 86.00\%$
(Pratt et al., 2016)	Kaggle	Total: 80,000	Features: Nil	CNN classifier: $A_{CC} = 75.00\%$ $S_{EN} = 30.00\%$ $S_{PEC} = 95.00\%$

2.3 Computer Aided Diagnosis System for Glaucoma

The various methods namely the morphological operations (Kolář & Jan, 2008; Nayak et al., 2009), nonlinear techniques (Maheshwari et al., 2017), textural features (Acharya et al., 2011; Mookiah et al., 2012; Noronha et al., 2014), statistical features (Acharya et al., 2015), and wavelet-based transforms (Dua et al., 2012; Maheshwari et al., 2017; Mookiah et al., 2012) are used for the classification of normal and glaucomatous fundus images.

⁹ University Malaya Medical Centre

Also, it can be noted that the support vector machine (SVM) is a common classifier used to classify normal and glaucoma class (Acharya et al., 2015; Bock et al., 2010; Dua et al., 2012; Kolář & Jan, 2008; Maheshwari et al., 2017; Mookiah et al., 2012). The SVM classifier is widely used in virtue of the simplicity nature of this classifier. Furthermore, the SVM is considered as it is one of the most efficient machine learning classifier model since the initiation of this algorithm (Karamizadeh et al., 2014).

Moreover, there are few researchers who graded the glaucomatous fundus images into normal, mild, and severe classes (Lim, 2014; Noronha et al., 2014). It can be seen from Table 2.3 that nonlinear (Noronha et al., 2014) and statistical features (Lim, 2014; Noronha et al., 2014) are used.

A glaucoma risk index (GRI) is also formulated to mathematically categorize normal from glaucomatous fundus images with an equation (Acharya et al., 2015; Bock et al., 2010; Mookiah et al., 2012).

Table 2.3: Summary of studies for automated screening system for normal and glaucoma classes using fundus images.

Author (Year)	Databases	Number of Images	Methods	Performance
Normal and Glaucoma				
(Kolář & Jan, 2008)	-	Normal: 14 Glaucoma: 16	Features: Retinal nerve fibres	SVM Classifier $A_{CC} = 93.80\%$
(Nayak et al., 2009)	-	Normal: 24 Glaucoma: 37	Features: Cup to disc ratio, optic nerve head shift, ISNT ratio	NN classifier: $A_{CC} = 93.00\%$ $S_{EN} = 90.00\%$ $S_{PEC} = 100.00\%$
(Bock et al., 2010)	EGR ¹⁰	Normal: 336 Glaucoma: 239	PCA, glaucoma risk index	SVM classifier: $AUC = 88.00\%$ $S_{EN} = 73.00\%$ $S_{PEC} = 85.00\%$
(Acharya et al., 2011)	KMC	Normal: 30 Glaucoma: 30	Features: HOS, GLCM	Random Forest classifier: $A_{CC} = 91.70\%$

¹⁰ Erlangen Glaucoma Registry

Author (Year)	Databases	Number of Images	Methods	Performance
(Dua et al., 2012)	KMC	Normal: 30 Glaucoma: 30	Features: DWT Consistency subset evaluation, chi-square, gain ratio, info gain	SVM Classifier $A_{CC} = 93.33\%$
(Mookiah et al., 2012)	KMC	Normal: 30 Glaucoma: 30	Features: Radon transform, HOS, DWT Glaucoma risk index	SVM classifier: HOS features: $A_{CC} = 68.33\%$ $S_{EN} = 80.00\%$ $S_{PEC} = 56.67\%$ Wavelet features: $A_{CC} = 90.00\%$ $S_{EN} = 86.67\%$ $S_{PEC} = 93.33\%$ HOS and wavelet features: $A_{CC} = 93.33\%$ $S_{EN} = 86.67\%$ $S_{PEC} = 93.33\%$
(Koh et al., 2013)	KMC	Normal: 30 Glaucoma: 30	Features: Relative wavelet entropy	SVM classifier: $A_{CC} = 93.33\%$ $S_{EN} = 93.33\%$ $S_{PEC} = 93.33\%$
(Yun & Koh, 2013)	KMC	Normal: 100 Glaucoma: 100	Features: Colour pixels values K-mean clustering	FS classifier: $A_{CC} = 92.00\%$ $S_{EN} = 85.00\%$ $S_{PEC} = 99.00\%$
(Yun et al., 2014)	KMC	Normal: 100 Glaucoma: 100	Features: DWT, fractal dimension, Brownian motion, energy, entropy	SVM classifier: $A_{CC} = 95.50\%$ $S_{EN} = 93.00\%$ $S_{PEC} = 98.00\%$
(Acharya et al., 2015)	KMC	Normal: 266 Glaucoma: 244	Features: Gabor transform, mean, variance, skewness, kurtosis, entropy, energy t-test, Bhattacharyya space, Wilcoxon test, ROC, entropy ranking, glaucoma risk index	SVM classifier: $A_{CC} = 93.10\%$ $S_{EN} = 89.75\%$ $S_{PEC} = 96.20\%$

Author (Year)	Databases	Number of Images	Methods	Performance
(Maheshwari et al., 2017)	KMC MIAG ¹¹	(KMC) Normal: 30 Glaucoma: 30 (MIAG) Normal: 255 Glaucoma: 250	Features: EWT, correntropy t-test, z-score, 3-fold, 10-fold	SVM classifier: (KMC) 3-fold cross-validation: $A_{CC} = 98.33\%$ $S_{EN} = 100.00\%$ $S_{PEC} = 96.67\%$ (MIAG) 3-fold cross-validation: $A_{CC} = 81.10\%$ $S_{EN} = 77.01\%$ $S_{PEC} = 84.31\%$
Normal, Mild and Moderate/Severe				
(Noronha et al., 2014)	KMC	Normal: 100 Mild: 72 Moderate/Severe: 100	Features: Radon Transform, higher order cumulant LDA	Naïve Bayes classifier: $A_{CC} = 92.65\%$ $S_{EN} = 100.00\%$ $S_{PEC} = 92.00\%$
(Lim, 2014)	KMC	NA	Features: mean, variance, skewness, kurtosis, entropies, and Gini index DWT	SVM classifier: $A_{CC} = 86.79\%$ $S_{EN} = 93.38\%$ $S_{PEC} = 95.10\%$

2.4 Computer Aided Diagnosis System for Abnormal (AMD, DR and Glaucoma) Classes

Few authors have proposed a retinal health eye screening system for an instant and reliable diagnosis of normal and abnormal retinal health using fundus images. Both works acquired their fundus images privately from Kasturba Medical College, India. It can be seen from Table 2.4, Bi-empirical mode decomposition (BEMD) (Acharya et al., 2016a) and the scalogram of 2-D continuous wavelet transform (CWT) (Koh et al., 2017a) are used. Also, entropy features are extracted in both studies. Entropy features can measure the pixels variation in the fundus images efficiently and capture sudden pixel changes in the images. Therefore, it is a popular feature extraction in fundus images.

¹¹ Medical Image Analysis Group (RIM ONE)

Additionally, a retinal risk index is developed (Acharya et al., 2016a) to mathematically differentiate normal and abnormal fundus images using a single number.

Furthermore, both works showed promising results with a high accuracy of 88.63% (Acharya et al., 2016a) and 92.48% (Koh et al., 2017a).

Table 2.4: Summary of studies for automated screening system for normal and abnormal classes using fundus images.

Author (Year)	Databases	Number of Images	Methods	Performance
(Acharya et al., 2016a)	KMC	Normal: 400 Abnormal: 400 (115 AMD, 170 DR, and 115 glaucoma)	Features: Bi-EMD, entropy Bhattacharyya distance, retinal risk index	SVM classifier: $A_{CC} = 88.63\%$ $S_{EN} = 86.25\%$ $= 91.00\%$
(Koh et al., 2017a)	KMC	Normal: 404 Abnormal: 1,082 (381 AMD, 195 DR, and 506 glaucoma)	Features: Scalogram of 2-D CWT, entropy, energy ADASYN, PSO	Random forest classifier: $A_{CC} = 92.48\%$ $S_{EN} = 89.37\%$ $S_{PEC} = 95.58\%$

In this chapter, the various automated detection algorithms are summarized in Table 2.1 to Table 2.4. Based on the literature review, it can be noted that very few work has been done on the detection of normal versus abnormal (AMD, DR and glaucoma) classes.

Therefore, the next two chapters, novel approaches to develop an automated CAD retinal health system are proposed. A two-class (normal and abnormal) and a four-class (normal, AMD, DR and glaucoma) problem are presented in the next two chapters.

Chapter Three

Two-class: Automated detection of retinal health using PHOG and SURF features extracted from fundus images

Many health-related problems rise with aging. One of the diseases that is prevalent among the elderly is the loss of sight. Various eye diseases namely AMD, DR, and glaucoma are the prime causes of vision loss as people grow old. Nevertheless, early detection of such eye diseases can impede the progression of this problem. Therefore, the elderly is encouraged to attend regular eye checkups for early detection of eye diseases. However, it is time-consuming and laborious to conduct a mass eye screening session frequently. Hence, a novel approach will be proposed to develop an automated retinal health screening system in this work. This work discusses a retinal screening system to automatically differentiate normal image from abnormal (AMD, DR, and glaucoma) fundus images. The fundus images are subjected to the pyramid histogram of oriented gradients (PHOG) and speeded up robust features (SURF) techniques. Then, the extracted data will be subjected to adaptive synthetic sampling to balance the number of data in the two classes (normal and abnormal). This proposed system will be user-friendly and robust retinal health screening system can be employed in mass eye screening and polyclinics. This will reduce the workload of clinicians in the main hospitals. In future, it is intended to extend this work to automatically classify the fundus images in to normal, AMD, DR and glaucoma classes.

3.1 Data Used

The fundus images were obtained from the Ophthalmology Department of Kasturba Medical College (KMC) in Manipal, India. These fundus images were taken with Zeiss FF450 plus mydriatic camera. A total of 1,804 fundus images were used in this work

(see Table 3.1). All the fundus images have a resolution of 360 x 480 pixels and stored in JPEG format. Further, the fundus images are grouped AMD, DR, and glaucoma classes as one group termed as abnormal. Figure 3.1 shows typical normal and abnormal fundus images.

Table 3.1: Number of fundus images used in each class.

Classes	Number of images
Normal	404
Abnormal	1,400
(AMD,	(529
DR, and	365
Glaucoma)	506)
Total	1,804

Figure 3.1: Typical fundus images of normal (top) and abnormal (bottom) classes.

3.2 Methodology

Figure 3.2 shows the workflow of the proposed method used to automatically detect normal and abnormal fundus images. In this work, the fundus images are first pre-processed then subjected to feature extraction. Subsequently, adaptive synthetic sampling (AdaSyn) was applied to balance the number of features in the two (normal and abnormal) classes. Then the features extracted from pyramid histogram of oriented

gradients (PHOG) and speeded up robust features (SURF) are fused using canonical correlation analysis (CCA). The particle swarm optimization (PSO) technique is used to select the optimum set of features to be fed into the classifier for classification.

Figure 3.2: Flowchart of proposed method to automatically detect normal and abnormal fundus images.

3.2.1 Pre-processing

The contrast limited adaptive histogram equalization (CLAHE) (Pizer et al., 1987) is applied onto the green layer of the fundus images. It improves the contrast of fundus images and at the same time, minimizes the noise present in the images (Wang et al., 2005). The fundus images are divided into segments and the histogram of each segment is computed. Then a clip limit depending on the desired contrast is obtained. Following that, the histogram in each segment is redistributed according to the clip limit. Finally, the gray scale mapping is done using cumulative distribution of histogram to get the enhanced image.

3.2.2 Feature Extraction

In this work, PHOG and SURF methods are applied on the fundus images to extract useful information for classification.

The PHOG is a feature descriptor used to epitomize the spatial patterns of the normal and abnormal fundus images (Bosch et al., 2007). The PHOG descriptor is particularly effective in represents the shapes in the images by the distribution and edge orientation in the histogram by canny-edge detector (Bosch et al., 2007). The fundus image is first divided into smaller cells and a histogram of edge orientations within the cell is computed. The computed histograms are combined as feature vector to be used for

describing the image (Bosch et al., 2007). Therefore, the PHOG can capture the characteristics of the fundus images very efficiently.

The SURF (Bay et al., 2008) descriptor describes the intensity distribution of an image. It uses a square-shaped filter (Haar wavelet filter) to pick up the subtle pixel changes within the image. Then, the orientation of the image is determined by convolving the pixels within the neighborhood using Haar wavelet filter (Bay et al., 2008). The Haar wavelet filter computes the intensity of the fundus image (Bay et al., 2008). Hence, it uses the change in intensities within the image to describe and represent the image. Therefore, the normal and abnormal fundus images are represented differently as the intensities in normal and abnormal fundus image are morphologically different. This is due to the presence of abnormal blood vessels, drusens, and lesions in the abnormal fundus image.

3.2.3 Adaptive Synthetic Sampling Approach (AdaSyn)

A disproportion of data samples in two or more classes has always existing big problem in machine learning (García et al., 2012). Further, it is noted that imbalance data in the two classes may affect the overall performance of the classifier.

AdaSyn (He et al., 2008) is adopted in this work to balance the number of features in normal and abnormal classes. The algorithm first determines the degree of imbalance in the normal and abnormal classes. Then it determines the number of samples to be synthesized. Figure 3.3 is a visual representation of the number of samples in the normal and abnormal class before and after applying AdaSyn. A total of 965 normal samples are generated with AdaSyn technique (see Table 3.2).

Table 3.2: Total number of fundus images used in two groups.

	Before AdaSyn	After AdaSyn
Normal	404	1,369
Abnormal	1,400	1,400

Figure 3.3: The distribution of images in normal and abnormal classes before and after AdaSyn.

3.2.4 Features Fusion

One single set of features is unable to yield optimal results therefore, two local descriptor features are fused in this work using the canonical correlation analysis (CCA) for this purpose. The CCA (Sun et al., 2005) is applied on the two set of features (PHOG and SURF) in this study. The transform matrix is multiplied with each of the feature set and then added together. The CCA then finds features between the two feature sets that have high similarities.

Assuming there are two matrices, $X \in \mathbb{R}^{p \times n}$ and $Y \in \mathbb{R}^{q \times n}$ each with n training vectors from two different methods. There are $(p + q) \times n$ features extracted.

The within-sets covariances matrices of x and y is denoted in equations 3.1 and 3.2 and the between-sets covariance matrices are denoted in equations 3.3 and 3.4.

$$S_{xx} = \mathbb{R}^{p \times p} \quad (3.1)$$

$$S_{yy} = \mathbb{R}^{q \times q} \quad (3.2)$$

$$S_{xy} = \mathbb{R}^{p \times q} \quad (3.3)$$

$$S_{yx} = S_{xy}^T \quad (3.4)$$

The overall $(p + q) \times (p + q)$ covariance matrix, S , contains all the information on the correlation between pairs of features as shown in equation 3.5.

$$S = \begin{pmatrix} cov(x) & cov(x, y) \\ cov(y, x) & cov(y) \end{pmatrix} = \begin{pmatrix} S_{xx} & S_{xy} \\ S_{yx} & S_{yy} \end{pmatrix} \quad (3.5)$$

CCA finds the linear combinations that maximize the pair-wise correlations across two data sets as these two feature vectors may not follow a consistent pattern and is difficult to understand the relationship between the two feature vectors (Haghighat et al., 2016; Krzanowski, 1988).

$$corr(X^*, Y^*) = \frac{cov(X^*, Y^*)}{\sqrt{var(X^*) \cdot var(Y^*)}} \quad (3.6)$$

where $X^* = W_x^T X$ and $Y^* = W_y^T Y$ is the linear combinations, $cov(X^*, Y^*) = W_x^T S_{xy} W_y$, $var(X^*) = W_x^T S_{xx} W_x$ and $var(Y^*) = W_y^T S_{yy} W_y$.

Lagrange multipliers is used for maximization by maximizing the covariance between X^* and Y^* with the constraints $var(X^*) = var(Y^*) = 1$ using equation 3.6. The transformation matrices, W_x and W_y is found by solving the eigenvalue equations 3.7 (Haghighat et al., 2016; Krzanowski, 1988):

$$\begin{cases} S_{xx}^{-1} S_{xx} S_{yy}^{-1} S_{yx} \widehat{W}_x = \Lambda^2 \widehat{W}_x \\ S_{yy}^{-1} S_{yy} S_{xx}^{-1} S_{xy} \widehat{W}_y = \Lambda^2 \widehat{W}_y \end{cases} \quad (3.7)$$

where $\widehat{W}_x$ and $\widehat{W}_y$ are eigenvectors and Λ^2 is the diagonal matrix of eigenvalues or squares of canonical correlations.

The transformation matrices, W_x and W_y consists of sorted eigenvectors corresponding to the non-zero eigenvalues. Equation 3.8 is known as canonical variates.

$$X^*, Y^* \in \mathbb{R}^{d \times n} \quad (3.8)$$

where $d = \text{rank}(S_{xy}) \leq \min(n, p, q)$ is the number of non-zero eigenvalues in equations 3.8, sorted in decreasing order $\lambda_1 \geq \lambda_2 \geq \dots \lambda_d$.

The sample covariance matrix defined in equation 3.5 will be of the form:

$$S = \begin{pmatrix} 1 & 0 & \dots & 0 & \lambda_1 & 0 & \dots & 0 \\ 0 & 1 & \dots & 0 & 0 & \lambda_2 & \dots & 0 \\ \vdots & & \ddots & & & & \ddots & \vdots \\ 0 & 0 & \dots & 1 & 0 & 0 & \dots & \lambda_d \\ \lambda_1 & 0 & \dots & 0 & 1 & 0 & \dots & 0 \\ 0 & \lambda_2 & \dots & 0 & 0 & 1 & \dots & 0 \\ \vdots & & \ddots & & & & \ddots & \vdots \\ 0 & 0 & \dots & \lambda_d & 0 & 0 & \dots & 1 \end{pmatrix}$$

From the above matrix, it can be shown that the canonical variates have non-zero correlation only with their corresponding indices and the identity matrices in the upper left and lower right corners shows that the canonical variates are uncorrelated within each data set.

Feature-level in this work is done by performing summation of the transformed feature vectors using equation 3.9 (Sun et al., 2005).

$$Z = X^* + Y^* = W_x^T X + W_y^T Y = \begin{pmatrix} W_x \\ W_y \end{pmatrix}^T \begin{pmatrix} X \\ Y \end{pmatrix} \quad (3.9)$$

where Z is called the Canonical Correlation Discriminant Features (Haghighat et al., 2016).

3.2.5 Feature Selection

Feature selection is an important process in machine learning (Piramuthu, 2004). If the features are not selected carefully, it may introduce more noise, redundancy or incomplete features to the classifier (Piramuthu, 2004). Thus, selecting an optimal feature set will improve the performance of the classifier. Hence, the particle swarm optimization (PSO) (Kennedy & Eberhart, 1995) technique is employed in this work to select the optimum set of features to be fed into the classifier.

PSO is an optimization technique originated by Eberhart and Kennedy in 1995 based on the behavioral study of birds (Kennedy & Eberhart, 1995). The underlying principle of PSO is the social interaction among each particle in a swarm. Every extracted feature models the behavior of a bird in the search space. These features also have their own fitness value and velocity parameter according to the fitness function. Then, the position and the velocity of each of the feature is updated accordingly. A subset of 10 is chosen in this work. Hence, only the top 10 features are selected in this work.

3.2.6 Classification

The k-nearest neighbor (kNN) classifier (Cover & Hart, 1967) is used in this work. It is a simple classifier which uses the minimum distance from the test data to the training data set to obtain the nearest neighbor (Cover & Hart, 1967). The k value of the nearest neighbor is varied from 5 to 25 and a maximum accuracy is obtained for $k = 5$ using 10-fold cross-validation technique. The results are validated using a 10-fold cross-validation strategy (Duda et al., 2001). The performance of the system is assessed based on the average accuracy, sensitivity, and specificity.

3.2.7 Confusion Matrix

A confusion matrix is often used to show the performance of a classifier model of a test data with known labels. In Table 3.3, there are 2 possible predictions: Normal and Abnormal. The classifier model predicted the test samples to be normal 55 times and abnormal 110 times, but only 105 test samples are abnormal.

The number of normal samples correctly predicted as normal is known as the True Negatives (TN), similarly, the number of abnormal samples correctly predicted as abnormal is True Positives (TP). The number of normal samples that are predicted as abnormal are known as False Positives (FP/Type I error) and the number of abnormal samples predicted as normal are False Negatives (FN/Type II error).

Table 3.3: Confusion matrix example

N=165		Prediction	
		Normal	Abnormal
Actual	Normal	50	10
	Abnormal	5	100

The performances used are calculated using the confusion matrix (Fawcett, 2005; Metz, 1978).

- Accuracy (ACC): $(TN + TP)/(TP + TN + FP + FN)$
- Positive Predictive Value (PPV): $TP/(TP + FP)$
- Sensitivity (SEN): $TP/(TP + FN)$
- Specificity (SPEC): $\frac{TN}{TN + FP}$

3.3 Results

A total of 111,272 features (680 PHOG and 110,592 SURF) are extracted in this work. Out of these 111,272 features, 505 features are obtained with CCA. Then, out of 505 features, 10 features are selected with PSO technique. Table 3.4 presents the mean and standard deviation values of these 10 selected features. From Table 3.4, it can be observed that the features for the two classes (normal and abnormal) are highly distinctive.

Table 3.5 is the summary of performances obtained with 10-fold cross-validation approach. The accuracy, sensitivity, and specificity obtained in each fold is high which shows the model to be stable.

Hence, an average accuracy, sensitivity, and specificity of 96.21%, 95.00%, and 97.42% respectively was obtained. Figure 3.4 shows the accuracy of each fold.

Table 3.4: Summary statistics of selected features for the two classes using particle swarm optimization (PSO).

	Normal		Abnormal		<i>p</i> -value	<i>t</i> -value
	<i>mean</i>	<i>sd</i> ¹²	<i>mean</i>	<i>sd</i>		
CCA80	-1.08x10 ⁻³	5.37x10 ⁻²	1.05x10 ⁻³	2.29x10 ⁻¹	0.7373	0.3355
CCA52	4.41x10 ⁻³	3.68x10 ⁻²	-4.31x10 ⁻³	2.32x10 ⁻¹	0.1695	1.3742
CCA111	-1.60x10 ⁻²	4.74x10 ⁻²	1.56x10 ⁻²	2.29x10 ⁻¹	0.0000	5.0067
CCA143	2.06x10 ⁻²	4.19x10 ⁻²	-2.01x10 ⁻²	2.29x10 ⁻¹	0.0000	6.4604
CCA129	-2.83x10 ⁻³	3.77x10 ⁻²	2.76x10 ⁻³	2.32x10 ⁻¹	0.3785	0.8809
CCA58	1.55x10 ⁻²	4.33x10 ⁻²	-1.52x10 ⁻²	2.30x10 ⁻¹	0.0000	4.8579
CCA63	1.84x10 ⁻²	4.79x10 ⁻²	-1.80x10 ⁻²	2.29x10 ⁻¹	0.0000	5.7767
CCA178	4.24x10 ⁻⁴	4.23x10 ⁻²	-4.14x10 ⁻⁴	2.31x10 ⁻¹	0.8950	0.1320
CCA74	-1.63x10 ⁻²	3.31x10 ⁻²	1.59x10 ⁻²	2.31x10 ⁻¹	0.0000	5.0962
CCA157	-1.09x10 ⁻²	3.63x10 ⁻²	1.07x10 ⁻²	2.32x10 ⁻¹	0.0007	3.4027

Table 3.5: Final results for 10-fold cross-validation.

Folds	TP	TN	FP	FN	ACC (%)	PPV (%)	SEN (%)	SPEC (%)
1	128	139	0	9	96.74	100.00	93.43	100.00
2	131	140	1	5	97.83	99.24	96.32	99.29
3	131	133	2	11	95.31	98.50	92.25	98.52
4	132	133	5	7	95.67	96.35	94.96	96.38
5	141	127	5	4	96.75	96.58	97.24	96.21
6	132	135	5	5	96.39	96.35	96.35	96.43
7	121	143	4	9	95.31	96.80	93.08	97.28
8	132	132	4	9	95.31	97.06	93.62	97.06
9	149	115	5	8	95.31	96.75	94.90	95.83
10	133	137	4	3	97.47	97.08	97.79	97.16
Average	133	133	3	7	96.21	97.47	95.00	97.42

¹² Standard deviation

Figure 3.4: Accuracy plot for 10-fold cross-validation.

Chapter Four

Four-class: Automated Retinal Health Diagnosis Using Pyramid Histogram of Visual Words and Fisher Vector Techniques

Untreated AMD, DR, and glaucoma may lead to irreversible vision loss. Hence, it is essential to have regular eye screening to detect these eye diseases at an early stage and to offer treatment where appropriate. One of the simplest, non-invasive and cost-effective techniques to screen the eyes is by using fundus photo imaging. But, the manual evaluation of fundus images is tedious and challenging. Further, the diagnosis made by ophthalmologists may be subjective. Therefore, an objective and novel algorithm using the pyramid histogram of visual words (PHOW) and Fisher vectors is proposed for the classification of fundus images into their respective eye conditions (normal, AMD, DR, and glaucoma). The proposed algorithm extract features which are represented as words. These features are built and encoded into a Fisher vector for classification using random forest classifier.

4.1 Data Used

The fundus images were acquired from the Ophthalmology Department of Kasturba Medical College in Manipal, India. In this work, 2,220 images with a resolution of 360 x 480, and they were captured with a Zeiss FF450 plus mydriatic camera using a field of view of 50° were used. Table 4.1 shows the number of fundus images used in each class. The fundus images were taken and labelled by experienced ophthalmologists from KMC, Manipal. Also, Figure 4.1 is a typical illustration of a normal, AMD, DR, and glaucoma fundus image.

Table 4.1: Number of fundus images used.

Classes	Number of fundus images
Normal	790
AMD	531
DR	346
Glaucoma	553
Total	2,220

Figure 4.1: Sample fundus images: (a) normal, (b) AMD, (c) DR, and (d) glaucoma.

4.2 Methodology

Figure 4.2 shows the flowchart of the proposed work. Firstly, PHOW are extracted from the fundus images, then Gaussian mixture model (GMM) is performed on the training set to obtain a vocabulary to encode the Fisher vectors for training and testing. PHOW, GMM and Fisher vector are implemented using VLFeat toolbox (Vedaldi & Fulkerson, 2010). Then the performance of this algorithm is determined with both blindfold and ten-fold cross-validation approach (classification).

Figure 4.2: The proposed method for the development of a CAD eye screening system.

4.2.1 Building Vocabulary and Features Extraction

The PHOW is employed in this work. It is a form of feature representation technique based on bag-of-words approach (Perronnin & Dance, 2007). The PHOW treats the image features as words. The colour fundus images are divided into a dense grid in steps of 2 with scales of 4, 6, 8, and 10. Then scale-invariant feature transform (SIFT) descriptors are extracted from the different scales as shown in Figure 4.3. The SIFT extracts the gradient and orientation around the neighborhood using equations 4.1 and 4.2 respectively. An orientation histogram is built from the neighborhood gradient orientations with 36 bins covering 360° and each point added to the histogram is weighted by its gradient magnitude. The orientation of the points is given by the peak of this histogram.

$$m(x, y) = \sqrt{(L(x+1, y) - L(x-1, y))^2 + (L(x, y+1) - L(x, y-1))^2} \quad (4.1)$$

$$\theta(x, y) = \tan^{-1} \frac{L(x, y+1) - L(x, y-1)}{L(x+1, y) - L(x-1, y)} \quad (4.2)$$

where $L(x, y)$ is the gaussian blurred image, m is magnitude and θ is the orientation.

Figure 4.3: Scale-invariant feature transform (SIFT) descriptors over scales of 4, 6, 8 and 10.

The descriptor vector is obtained using 4x4 grid centered over each point orientated to the point orientation and orientation histogram in 8 directions is calculated for all 16 grids. The descriptor is normalized to unit length and a threshold of 0.2 is applied to reduced influences from large gradient magnitudes and renormalized. Finally, a random selection of 100,000 sub-set of columns was selected to build the vocabulary. The Gaussian mixture model (GMM) is then applied to find the mean, diagonal covariance, and prior probabilities of the GMM. Subsequently, the extracted vocabulary is used to encode improved Fisher vector. The power normalization or signed square-rooting is used to “un-sparsify” the vector to keep the dot-product similarity by making the distribution of features less peaky around zero (Niemeijer et al., 2009; Perronnin & Larlus, 2015). Also, the L2 normalization, which is the square root of the sum of the squares of the absolute values, is used to cancel the effect of dependency on image specific information (Perronnin et al., 2010).

In this work, both experiments build up the vocabulary from PHOW feature extraction. After that, the Fisher vector (Uchida et al., 2013) is used to generate the vector (representation of the fundus image).

4.2.2 Fisher Vector

The Fisher vector (Uchida et al., 2013) encoding is based on the Fisher kernel which groups a dense set of local features into a high-dimensional descriptor representing the image-level features. The descriptors use the gradient, based on probability density function to calculate the log-likelihood of the local features. The gradient is assumed to follow a GMM model to approximate the Fisher information. Fisher vector not only considers the gradient with respect to the weights but also the derivatives with respect to the mean and standard deviation (Perronnin & Dance, 2007). Thus, it encodes the number of occurrences of each visual word with additional information about the

distribution of the descriptors for the same vocabulary size. Using the 500 GMM cluster centers, the Fisher vector are encoded based on the differences between the image descriptors and centers. Thus, distinct features extracted from the four classes (normal, AMD, DR, and glaucoma) are encoded into the Fisher vector for classification.

4.2.3 Adaptive Synthetic Data Sampling (AdaSyn)

It can be seen from Table 4.2 that the distribution of data for the four classes (normal, AMD, DR, and glaucoma) is unequal. Therefore, AdaSyn is applied to the fundus images to make the number of training data (features) to be equal in four different classes. AdaSyn (He et al., 2008) is an algorithm which generates synthetic data to balance the number of data in each class. Firstly, the algorithm decides the extent of imbalance in the four classes then it computes the number of data to be generated. The algorithm randomly selects a sample from the minority class and uses its k-nearest neighbours to generate several synthetic samples.

4.2.4 Classification

The random forest (RF) classifier (Breiman, 2001) was employed as the classifier in this work. It is an ensemble learning algorithm for classification. This algorithm is based on the classification outputs made from a set of decision trees. Each decision tree will determine the output and the final decision is based on the majority votes. 500 decision trees were used to determine the class. Also, ten-fold cross-validation (Duda et al., 2001) and blindfold (Devroye & Wagner, 1979) strategies were employed to validate the proposed algorithm.

Table 4.2 records the total number of fundus images used for the training and testing of the proposed algorithm. The data is randomly split into training and testing set. 70% of the minimum class is used and the same number of images are randomly sampled

from the other classes. The same is done with the 80% and 90% dataset splits. Figure 4.4 shows the out-of-bag classification error for the 90% training set.

Table 4.2: The number of fundus images used in different percentage split for the blindfold approach.

Data Split (%)	Training	Testing
70	Normal: 242	Normal: 548
	AMD: 242	AMD: 289
	DR: 242	DR: 104
	Glaucoma: 242	Glaucoma: 311
80	Normal: 277	Normal: 513
	AMD: 277	AMD: 254
	DR: 277	DR: 69
	Glaucoma: 277	Glaucoma: 276
90	Normal: 311	Normal: 479
	AMD: 311	AMD: 220
	DR: 311	DR: 35
	Glaucoma: 311	Glaucoma: 242

Figure 4.4: Out-of-bag classification error plot for 90% training set.

4.3 Results

Table 4.3 and Table 4.4 present the results using the ten-fold cross-validation (balanced dataset) and blindfold (unbalanced dataset) respectively. Three different performance results are obtained using 70%, 80%, and 90% data split respectively. It can be noted that the overall diagnostic accuracy for both validation techniques regardless of percentage split is relatively high.

It can be seen from Table 4.3 that the highest accuracy of 96.79% is obtained from 90% data split for the unbalanced dataset. Similarly, the highest accuracy of 90.06% is obtained from the 90% data split for unbalanced dataset as listed in Table 4.4.

From the confusion matrices provided in Table 4.5, it can be observed that regardless of data splits (70%, 80%, or 90%) more DR images are misclassified as AMD. This might be due to the similarities between drusens (in AMD) and exudates (in DR). In addition, it can be observed that the proposed algorithm works well for glaucoma class.

Table 4.3: Results using ten-fold cross-validation (balanced dataset).

Data Split (%)	TP	TN	FP	FN	ACC (%)	PPV (%)	SEN (%)	SPEC (%)
70	2287	753	37	88	96.05	98.41	96.29	95.32
80	2295	756	34	80	96.39	98.54	96.63	95.70
90	2306	766	24	78	96.79	98.97	96.73	96.96

Table 4.4: Results using blindfold validation (unbalanced dataset).

Data Split (%)	TP	TN	FP	FN	ACC (%)	PPV (%)	SEN (%)	SPEC (%)
70	623	503	45	81	89.94	93.26	88.49	91.79
80	524	464	49	75	88.85	91.45	87.48	90.45
90	438	441	38	59	90.06	92.02	88.13	82.07

Table 4.5: Confusion Matrix using blindfold validation (unbalanced dataset).

70%		Ground Truth			
		Normal	AMD	DR	Glaucoma
Predicted	Normal	503	11	3	13
	AMD	28	242	10	6
	DR	14	30	91	2
	Glaucoma	3	6	0	290

80%		Ground Truth			
		Normal	AMD	DR	Glaucoma
Predicted	Normal	464	12	1	13
	AMD	43	208	6	3
	DR	2	27	59	3
	Glaucoma	4	7	3	257

90%		Ground Truth			
		Normal	AMD	DR	Glaucoma
Predicted	Normal	441	12	1	12
	AMD	28	187	2	9
	DR	7	16	32	2
	Glaucoma	3	5	0	219

Chapter Five

Discussion

In this thesis, two novel methods were developed to classify (i) normal and abnormal; (ii) normal, AMD, DR and glaucoma classes. The discussion of the classification of normal and abnormal classes will be noted in Section 5.1 and the four classes will be discussed in Section 5.2.

5.1 Classification of two-classes

It can be noted from Table 3.4 that; the features are unique and differentiable. This is because PHOG descriptor reveals the spread of edge and gradient intensities present in the fundus images (Bosch et al., 2007). Further, the SURF descriptor also describes the intensity distribution of pixels within its neighboring pixels in the fundus images (Bay et al., 2008). Therefore, the highly-correlated features combined with CCA improve the recognition performance (Sun et al., 2005). The different features (PHOG and SURF) extracted contain various information characteristics in the fundus images. So, the fusion of mutual features will boost the classification performance.

The PSO technique is used in this work to appropriately search the optimal set of features with lesser computational complexity. This has helped to obtain the highest classification performance using least number of features.

The main feature of this study is that, the highest performance obtained using blind-fold cross validation which is close to the real-world applications in which samples tested are unknown to the model.

5.2 Classification of four-classes

In this current work, a novel technique is proposed by implementing PHOW to describe the fundus images with Fisher vector using visual vocabularies for the classification of the various eye conditions. The highest diagnostic accuracy of 96.79% using the ten-fold cross-validation was achieved and obtained 90.06% classification accuracy with blindfold validation.

Further, the diagnostic performance has improved from the previous work published in 2016 to the subsequent works until the presently proposed CAD system (see Table 5.1). Moreover, the number of fundus images used have increased. In Acharya et al. (Acharya et al., 2016a), there were only 800 (400 normal and 400 abnormal) fundus images whereas the current work consists a total of 1,804 fundus images.

Given the high performance in this work, it can be noted that the PHOW can represent the frequency of word occurrence in the fundus images accurately. It can pick up the subtle variations recurring in the pixels of the images and build the vocabulary which can categorize the fundus images accordingly into their respective classes. Moreover, this method is resistant towards the orientation and position of the features (Bosch et al., 2007). Hence, 90.06% classification accuracy was obtained with blindfold validation.

In Chapter Three, the different eye conditions were grouped as one abnormal class. In this study, the CAD eye screening system can identify the different eye abnormalities (AMD, DR, and glaucoma) individually. Thus, able to assist the ophthalmologists to provide a reliable diagnosis of each eye class.

Furthermore, the published works documented in Table 5.1 validated their algorithms with ten-fold cross-validation. In this work, both ten-fold and blindfold validation were performed. It is observed that the proposed algorithm yielded the highest

diagnostic performance with the ten-fold cross-validation. Besides, it can be noted that using the ten-fold strategy (balanced dataset) achieved the better performance due to the application of AdaSyn strategy before training of the features. AdaSyn balances the number of data in each class, and therefore, there is an increase in the overall number of data for training and testing of the proposed algorithm. With more number of synthetic data generated, there are more data to train the algorithm and hence, this increased in diagnostic performance using the ten-fold approach.

Having a mass screening program will also create awareness of various eye diseases and the importance of an early detection of any eye conditions. Besides, the CAD system can be installed in polyclinics to assist healthcare professionals in the initial diagnosis of the eye and issue referral only to patients with diseased eyes. This way, the workload of ophthalmologists in hospitals will reduce, and ophthalmologists can focus more on patients requiring immediate medical attention.

The developed system can be used by general practitioners and at polyclinics. The clinicians can refer only the abnormal class (AMD, DR or glaucoma) to the main hospital ophthalmology department for further confirmation and treatment. Therefore, our CAD eye screening system can help to alleviate the workload of the ophthalmologists in eye screening and assist in making accurate diagnosis.

The proposed algorithm was not run on public database, as there are no public database comprising of all four classes (normal, AMD, DR and glaucoma) of images. So, images from four different databases with different resolutions and field of views which may not yield good classification results. Hence, there is intention to employ deep learning techniques to diagnose the various eye conditions in future work.

Table 5.1: Selected studies of CAD system to automatically detect the various eye conditions.

Authors	Year	Number of images	Methods	A_{CC} (%)	S_{EN} (%)	S_{PEC} (%)
2-class (normal and abnormal)						
(Acharya et al., 2016a)	2016	Normal: 400 Abnormal: 400 (115 AMD, 170 DR, 115 glaucoma)	Bi-dimensional empirical mode decomposition entropies Chernoff bound Bhattacharyya distance Support vector machine classifier (10-fold cross-validation) Retinal risk index	88.63	86.25	91.00
(Koh et al., 2017a)	2017	Normal: 404 Abnormal: 1,082 (381 AMD, 195 DR, 506 glaucoma)	Continuous wavelet transforms, entropies, energy AdaSyn, Particle swarm optimization RF classifier (10-fold cross-validation)	92.48	89.37	95.58
(Koh et al., 2017c)	2017	Normal: 404 Abnormal: 1,400 (529 AMD, 365 DR, 506 glaucoma)	Pyramid histogram of oriented gradients, Speeded up robust features AdaSyn, Canonical correlation analysis, Particle swarm optimization K-nearest neighbour classifier (10-fold cross-validation)	96.21	95.00	97.42

Authors	Year	Number of images	Methods	A_{CC} (%)	S_{EN} (%)	S_{PEC} (%)
4-class (normal, AMD, DR, and glaucoma)						
Present work (Koh et al., 2017b)	2017	Normal: 790	PHOW,	10-fold:	10-fold:	10-fold:
		AMD: 531	GMM,	96.79	96.73	96.96
		DR: 346	Fisher vector,			
		Glaucoma: 553	AdaSyn	Blindfold: 90.06	Blindfold: 88.13	Blindfold: 82.07
			RF classifier (10-fold cross- validation and blindfold)			

The benefits of the proposed algorithm:

- (i) No pre-processing of the fundus images.
- (ii) It is validated with both ten-fold and blindfold strategies.
- (iii) It can be used to assist the clinicians to cross-check their decision on the eye screening.
- (iv) Used maximum number of images in Table 5.1 and obtained the highest performance.

The drawbacks of the proposed algorithm include:

- (i) It is computationally intensive as we need to generate the vocabulary from the data.
- (ii) More fundus images are needed to boost the performance of the proposed algorithm.

Chapter Six

Conclusion & Future Work

6.1 Conclusion

In this thesis, a diagnosis support system for the classification of normal and abnormal eye is proposed. Then also for the first time a completely automated system to classify four-classes namely normal, AMD, DR and glaucoma is performed. The summary of the thesis is as follows:

Automated diagnosis of normal and abnormal classes demonstrates an effective automated eye screening algorithm with an accuracy of 96.79%, sensitivity of 96.73% and specificity of 96.96% for four class using 10-fold cross validation. Based on the high performance obtained in this work, the proposed algorithm can be utilized in the clinical settings for an automated eye screening. This user-friendly and robust retinal health screening system can be employed in mass eye screening and polyclinics. This will reduce the workload of clinicians in the main hospitals.

An original approach to develop a CAD eye screening system for the detection of various eye diseases (normal, AMD, DR and glaucoma) is proposed in this work. Blindfold and ten-fold cross-validation techniques are implemented in this study. This proposed work is an extension of our previous studies (Table 5.1). Therefore, it is an innovative approach, and the first work to the best of found knowledge proposed to assist the ophthalmologists in making an accurate diagnosis of the various eye conditions by providing an adjunct tool. Our proposed CAD system can be placed in third world countries and remote villages where the healthcare services are limited. Additionally, the proposed CAD eye system can be used to conduct a mass eye screening session for the elderly as an early detection of any eye abnormality. The

performance of the system can be further improved by taking more diverse images in each class. Also, this proposed technique can be used to detect other eye diseases like diabetes maculopathy, floaters, retinal detachment and macular hole.

The main contributions of the thesis are:

- (i) Automated detection of retinal health using PHOG and SURF features extracted from fundus images. The proposed method can classify the normal and abnormal (AMD, DR, and glaucoma) classes (Chapter Three) accurately. Such a system can be installed in polyclinics and general practitioner's clinics. It will help to screen the abnormal eye and as a result the normal subjects will not be going to the main hospitals to screen their eyes.
- (ii) Automated retinal health diagnosis using pyramid histogram of visual words and Fisher vector techniques. The normal, AMD, DR and glaucoma images are classified using nonlinear methods with fundus images (Chapter Four). This is the first work proposed to classify the four classes. It will help the clinicians significantly to alleviate their workload and provide timely treatment.

6.2 Future Work

The future work of the thesis is given below:

- (i) The performance of the proposed system can be improved by using more subjects in each class. The classification instead of ten-fold cross validation, subject specific need to be implemented.
- (ii) Early stage of DR, glaucoma and AMD need to be focused.
- (iii) Integrated index can be developed using the features extracted from the fundus images. It will help to discriminate the four classes using a single integer.

- (iv) Deep learning techniques can be used to improve these methods. There is intention to extend this work to automatically classify the fundus images in to normal and abnormal classes using deep learning, where entire image is used without any pre-processing, feature extraction, and classification. The model automatically gets trained with the input images and classifies. Hence, image segmentation and feature extraction and selection of feature ranking methods and classifiers are not required.

A brief explanation on this is provided below.

6.2.1 Convolution Neural Network (CNN)

CNN is a form of artificial neural network inspired by biological processes. Neural networks are originated from biological stimulation (Lee et al., 2017). A neuron is a biological cell that processes information. It is made up of axon, a cell body, dendrites, nucleus, and synapses (Lee et al., 2017). The activation function in the artificial neuron acts as the nucleus in a biological neuron whereas the input signals and its respective weights represent the dendrites and synapses respectively in a biological neuron. Furthermore, the output of other neurons behaves as an axon in the biological neuron (see Figure 6.1). The neurons interconnect with each other to transmit information. Therefore, in an artificial neural network (ANN), the network consists of many artificial neurons where each neuron is a computing unit on its own. Generally, an ANN has three layers – the input layer, hidden layer, and an output layer (see Figure 6.2). However, ANN is susceptible to shift and translation distortion therefore, an improved version called the CNN is developed. CNN is both shift and translational invariance. Also, implementing CNN in medical images have been on the rise (Hatipoglu & Bilgin, 2017; Kallenberg et al., 2016; Pereira et al., 2016; Setio et al., 2016; Tan et al., 2017).

Figure 6.1: Axon in biological neuron

Figure 6.2: Neurons in Artificial Neural Network

Tan et al. (Tan et al., 2017) implemented CNN to segment blood vessels, fovea, and optic disc from fundus images. They have reported the highest accuracy of 94.54%. There is no need to perform feature extraction, feature selection, ranking and classification while using deep learning. The image features are learnt by the CNN and overcome the burden of conventional classification system involving selection of optimal features required to get the highest performance while able to classify accurately. Usually, the optimum parameters are achieved by trial and error method. Pratt et al. (Pratt et al., 2016) had used CNN to classify fundus images with an accuracy of 75%.

Typically, CNN model has four different layers: (1) convolutional layer, (2) nonlinear layer, (3) pooling layer, and (4) fully connected layer (Lee et al., 2017; Yann et al., 2015; Zhao et al., 2017).

6.2.1.1 Convolution Layer

Convolution layer is the first layer of any CNN. Filter slides along the image, multiplies the values in the filter with the pixel values of the image and sum to a single number. This number is mapped into a feature map (Yann et al., 2015)

6.2.1.2 Nonlinear Layer

It is conventional to insert a nonlinear or activation layer after the convolution layer to introduce nonlinearity into the system. It is found that the rectified linear unit (ReLU) layers works better over tanh and sigmoid layers, significant cutting the training time and reduce the vanishing gradient problem, where the gradient reduce exponentially lead to slow training of the lower layers of the network (Krizhevsky et al., 2012; Nair & Hinton, 2010; Yann et al., 2015).

6.2.1.3 Pooling Layer

Pooling layer down samples the output from the ReLU layer, reduces overfitting and lessen computation cost by reducing the spatial dimension of the input volume. The pooling methods commonly used are max, average and L2-norm pooling (Yann et al., 2015).

6.2.1.4 Fully Connected Layer

Fully Connected layer takes the output from the previous layer as input and output N dimensional vector where N is the number of classes in the data. This layer looks at the output of the previous layers and determine which class the features strongly correlate with (Yann et al., 2015).

6.2.2 Deep Belief Network (DBN)

On the other hand, DBN is a stack of Restricted Boltzmann Machines (RBM) with a single layer of feature detecting units. RBM consists of two-layers, visible and hidden as shown in Figure 6.3. Each node learns a single feature from the data by making random decision on whether to transmit the input or not.

Adbel-Zaher & Eldeib (Abdel-Zaher & Eldeib, 2016) employed DBN with neural network to classify breast cancer images from the Wisconsin Breast Cancer Dataset (WBCD) with an accuracy of 99.68%.

Figure 6.3: Restricted Boltzmann Machine

6.2.2.1 Restricted Boltzmann Machine

Each layer of RBM is bidirectional connected, undirected graphical model. By stacking RBM, higher level pattern representations can be extracted from representations from the previous layer in an unsupervised manner (Fischer & Igel, 2012; Hinton et al., 2006; Schmidhuber, 2015). RBM can be extended to output labels for each observation and fine-tuned using normal supervised learning algorithms. This generative model based pre-training of the weights allow problems observed in training multi-layer neural network to be overcome (Fischer & Igel, 2012).

Sampling methods, such as contrastive divergence (CD), persistent contrastive divergence (PCD) and parallel tempering (PT), are used to reduce the computationally intensive process of finding the likelihood of an undirected model or its gradient for inference (Fischer & Igel, 2012).

The implementation of deep learning will be able to reduce the workload of clinicians in hospital by screening for eye diseases in polyclinics. Deep learning can be

used to screen for eye diseases without feature extraction and selection and to prevent overfitting, the image data is artificially increased by augmentation (Krizhevsky et al., 2012). Deep learning has been shown to be able to classify many classes (Krizhevsky et al., 2012; Simonyan & Zisserman, 2014), thus the system can be expanded to classify normal, AMD, DR and glaucoma images as individual classes.

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Appendix A: Published Papers

Koh, J. E. W., Ng, E. Y. K., Bhandary, S. V., Laude, A., & Acharya, U. R. (2017c).

Automated detection of retinal health using PHOG and SURF features extracted from fundus images. *Applied Intelligence*, 1–15.

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