Detecting glaucoma in biomedical data using image processing

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Detecting Glaucoma in biomedical data using image processing

By

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Abstract

This thesis addresses the problem of the early detection of an eye blinding disease, glaucoma. It presents new approaches for analysis of the biomedical scan data of Retinal Nerve Fiber Layer (RNFL) thickness obtained through Scanning Laser Polarimetry that can lead to better tools for early diagnoses of glaucoma. The thickness maps of the RNFL obtained from a Scanning Laser Polarimeter (Gdx-VCC) were used to draw features as opposed to the circular ring one-dimensional data (TSNIT graph) in previous approaches. Fourier analysis and wavelet analysis were performed on the 90° projections of the thickness map data to emphasize the shape contained in the RNFL around the optic disc. Another approach was to analyze the shape of the entire 2 dimensional thickness maps through 2D Fourier Transform. A pattern image based on the shapes observed in the scans was generated and used to draw features. Principal Component Analysis was performed on the combined feature set for dimension reduction of feature space. Finally Fisher’s linear discriminant function (LDF) was used as a classifier. A Receiver Operating Characteristic (ROC) curve analysis of the developed parameters has been performed for all the feature sets used and has been compared with one of the currently used technique of Fourier analysis of TSNIT graph data available from similar eye scan images. The analysis tools implemented and used for the classification gives comparable results with the existing techniques and hence offer an effective tool for enhancing diagnostic abilities and can add to the sensitivity of the existing techniques to improve performance.
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Chapter 1

Introduction

Glaucoma encompasses a variety of diseases and conditions. It is a group of optic nerve diseases, with ‘characteristic’ progressive structural changes leading to loss of visual function in a ‘characteristic’ way.\textsuperscript{1} Glaucoma is the second leading cause of blindness worldwide.\textsuperscript{2, 3} The retina is the innermost layer in the eye and the retinal nerve fibers transmit the visual signal from the photoreceptors in the eye to the brain via the bundle going out of the eye, known as the optic nerve. Glaucoma leads to continuous and speedy damage of the retinal nerve fiber layer and hence can lead to permanent blindness. The progression of the nerve fiber layer loss can be effectively stopped by treatment
consisting of medication or surgery to reduce the intraocular pressure. Hence the diagnosis of glaucoma at an earlier stage is very important for its treatment.

A major concern with glaucoma detection is that the disease has no particular set of physical causes or symptoms that doctors can recognize to detect the disease in an early stage.\(^4\) The main focus in glaucoma diagnosis is to detect changes in the visual functioning of the eye at early stages of the disease so that vision can be protected and preserved through medical treatment. It has been proved that the development of visual field defects is preceded by RNFL damage in glaucoma.\(^5\) Studies show that as much as 40% of retinal nerve fiber in the eye can be lost without the detection of characteristic visual defect in glaucoma patients.\(^6\) Hence it is believed that the detection of damage in nerve fiber layer can lead to an early detection of glaucoma. Several computer-assisted imaging technologies for detecting the structural changes in the retinal nerve fiber layer have been developed. The assessment of the ganglion cell structure is based on measuring the thickness of the retinal nerve fiber layer.

One such device, the Scanning Laser Polarimeter (GDx-VCC, Laser Diagnostic Technologies, Inc., San Diego, CA) is based on the principle of measuring the change in the polarization of light exiting the eye (Fig. 1.1). The retinal nerve fiber layer consists of parallel structures of diameter smaller than the wavelength of light, which makes it a birefringent structure. A birefringent structure has the ability to change the polarization of polarized light double passing it.\(^7\) The amount of change in the state of polarization (retardation) can be accessed with a polarimeter. In this case, the retardation is the
measurable phase shift of polarized laser beam double passing the RNFL. This is found to be proportional to the thickness of the nerve fiber layer.\textsuperscript{8, 9} This retardation (degrees) information is converted to thickness (microns) through the conversion factor based on the histologic comparison with monkey eyes.\textsuperscript{10} A new version of the device (GDx-VCC) is designed to individually compensate for the effects of birefringent properties of other parts of the eye like the cornea. The device provides a large array of points corresponding to retinal nerve fiber layer thickness at each respective point across the back of the eye. The scans thus available are in the form of 128 X 256 images or gray-level thickness maps. The goal of this thesis is to analyze these scans and develop classification techniques for them.

![Photograph of a Scanning Laser Polarimetry Device](Figure 1.1)

\textit{Figure 1.1} Photograph of a Scanning Laser Polarimetry Device  
(Courtesy: Laser Diagnostics, San Diego, CA)

The first step in a classification problem is to extract useful features from the set of given data. The original scan is used to derive patterns or features that can separate the two classes. The feature extraction step is to obtain a feature vector, a set of different useful features, which reduce the dimension of the original data while keeping all the essential information contained in the data. The next step after obtaining distinguishable
and reliable set of features is to make them statistically independent. A very effective way to achieve this end is to perform Principal component analysis on the feature set\textsuperscript{11}. This will help in reducing feature dimension by eliminating redundancy caused by interdependencies in the feature vector. The last step is the classification of the data set into the two classes. Fisher’s Linear Discriminant Analysis (LDF) provides an easy and robust way of linearly classifying different classes by projecting the feature vector so that it maximizes class separability\textsuperscript{12}.

**Previous Work:**

The Scanning laser polarimetry devices provide a number of software-generated parameters, the main ones being the software generated parameters as ‘the number’ and the ‘NFI’ (nerve fiber indicator). Reports have shown that GDx software generated parameters have limited ability for glaucoma detection\textsuperscript{13-23}. Several other approaches for the analysis of the scan data available through these devices have been presented to improve upon these results. Locally based techniques like relative surface height\textsuperscript{17} and sectoral-based analysis\textsuperscript{18} have been reported with better results than GDx parameters. One approach proposed a linear discriminant function combining GDx parameters and found better result than the ‘number’\textsuperscript{16}. Another approach proposed discriminant analysis of 30\textdegree sectoral data from the scanning laser polarimetry\textsuperscript{19}. A lot of proposed techniques use the data obtained from a circular ring band around the center of the optic disc in the scan data. The inner radius of the ring is taken to be 1.75 times the disc diameter\textsuperscript{20}. A double hump pattern has been reported to exist in the one-dimensional data thus obtained\textsuperscript{21}. Most of the algorithms analyze the changes in the double hump pattern using
different techniques. In some more robust approaches the global shape analysis of the
double hump curve has been suggested and found to better in identifying glaucomatous
patients. These techniques include Fourier analysis suggested with different number of
sampling as well as different combinations of the Fourier analysis components.\textsuperscript{19-22}
Wavelet-Fourier analysis of the one-dimensional data has also been proposed and shown
to have better identification power as compared with the ‘number’.\textsuperscript{23}

The techniques used currently for the analysis of the scan data from the Scanning
laser polarimetry devices have chiefly depended on the ring data around the optic disc
center. The scan is divided into four sectors known as the Temporal, Superior, Nasal, and
Inferior and hence the data obtained from the ring around the optic disc is called the
TSNIT graph. Although these data provide considerable amount of information for
glaucoma recognition, the information in the rest of the scanned image must not be
completely neglected. In order to further improve the performance of the classifier,
Fourier analysis of the data obtained using the entire region of the scan as well as analysis
of the two dimensional Fourier transform of the scan is proposed.

This thesis presents a unique approach to the analysis of data from scanning laser
polarimetry devices by using the entire data in the retinal scan data as an image to
generate useful feature vectors. Techniques like taking different angular projections
(Radon Transform) of the image (scan data), 2D Fourier Transform and correlation of the
scan images with observed pattern images are proposed.
Chapter two provides a brief description and discussion of the disease in question. The third chapter explains concisely the physics of the scanning laser polarimetry device used to obtain the data and gives a brief history of the analysis methods previously used for the scan data. The first phase of the thesis will mainly focus on generation and selection of the useful features through experimentation on available data. The fourth chapter discusses the features that were finally chosen to formulate the classification system. After the selection of final set of features, the feature optimization and final classification steps are explained and discussed in chapter five. Once the recognition system is realized, the ROC curve analysis is used for the performance evaluation of the proposed analysis algorithm and comparison with one of the previous algorithms using global analysis of the one dimensional ring data are presented in chapter six. The conclusions are discussed in chapter seven. The appendix has parts of the code attached for obtaining the discussed features, their PCA analysis, LDF classification as well as the ROC analysis.
Chapter 2

Glaucoma

The term ‘glaucoma’ refers to a large number of optic nerve diseases, which is associated with loss of visual activity and can lead to total, irreversible blindness if left untreated\textsuperscript{24}. Glaucomatous optic neuropathy is the second leading cause of blindness worldwide.

The optic nerve is a cylindrical structure responsible for carrying the visual information out of the eye towards the brain. (Figure 2.1) Neural fibers, the primary component of the optic nerve, are composed of about 1.2-1.5 million ganglion cell axons.
These axons originating in the ganglion cell layer of the retina, the innermost layer of the eye, form the retinal nerve fiber layer (RNFL). These axons collect the visual information and carry it outside the eye via the optic nerve. The nerve head is the distal portion of the optic nerve. The retinal nerves converge upon the nerve head from all points of the fundus. The portion of the optic nerve head that is clinically visible by an ophthalmoscope is known as the optic disc. The optic nerve head is slightly vertically oval and it is also the site of entry for the retinal vessels. The shape and size of the optic disc is important in evaluation for glaucoma diagnosis.

Figure 2.1 Anatomy of the eye
(Courtesy: Handbook of Glaucoma (Azuara-Blanco Augusto))

Intraocular Pressure (IOP) is a result of complex interplay of components of the aqueous humor dynamics in the eye. It describes the pressure in the eye due to production and flow of optic fluid known as aqueous humor. A ‘normal’ IOP (that does not lead to
Glaucomatous damage) is usually defined as 15.5 + 2.5 mmHg while ‘glaucomatous’ IOP is generally described as above 20.5 mmHg. However, glaucoma patients are known to have IOP within the normal range and raised IOP can be found in non-glaucomatous eyes. Intraocular pressure is subject to a certain daily variation as well as variation during the same day. Normal eyes show less diurnal variation in the IOP than glaucomatous eyes. The elevated IOP when beyond that compatible with normal ocular function leads to irreversible damage to the nerve fibers in the retina, thus causing visual impairment. Intraocular pressure has a central role in the treatment of all forms of glaucoma today. It has been considered the main risk factor for glaucoma, and almost every treatment for glaucoma patient is aimed at reducing the IOP. Although raised IOP is considered a big risk factor for glaucoma, alone it is insufficient for the diagnosis of most forms of glaucoma. It has been associated with only 50% sensitivity and 90% specificity. However it still is the primary criterion for making diagnosis for patients with normal optic nerve heads and normal visual fields as well as in cases of congenital and secondary glaucoma. The most widely used and accepted gold standard for measuring IOP is Goldmann tonometry. Goldmann determined that when an area of 3.06 mm in a human eye is flattened with 520 µm corneal thickness, then resistance of cornea balances with the surface tension and hence could be ignored. This is the main principle on which the tonometer is based.

Glaucoma can cause damage to the optic nerve in a variety of ways. It has been proved that irrespective of the type of damage, the development of visual field defects is always preceded by optic nerve damage in glaucoma. The appearance of the optic disc is
a very important characteristic to determine glaucomatous damage. The shape of the optic disc in a normal eye is round or horizontally oval. The region in the retina around the optic disc has been divided into four areas, the horizontal sector towards the nose is called the Nasal region, the other horizontal sector being the Temporal, the vertical sector above the disc is known as Superior while the sector below is called Inferior (Figure 2.2). The neural rim around the optic disc is widest in the inferior quadrant, followed by superior, nasal and temporal.

There are various patterns of optic disc changes in glaucoma, and the detection of change is the diagnosis of glaucoma. The concentric enlargement of the optic cup, notching, and other similar patterns of glaucomatous damage are the most commonly found. The optic disc to optic cup ratio is therefore usually taken into consideration while evaluation. However the asymmetries of cup/disc can have other diseases as a cause and are therefore not as reliable. Other features taken into account are the size and shape of

![Figure 2.2](image)

*Figure 2.2* Photograph of the optic nerve with optic disc in the center and the areas around it divided into the four sectors – Temporal, Superior, Nasal, and Inferior.

the rim around the optic disc and the presence of optic disc hemorrhage. To examine the shape of the optic disc for glaucomatous changes, ophthalmoscope is generally used. The
direct examination of the optic disc through an ophthalmoscope is called ophthalmoscopy and it can provide useful information for diagnosis of glaucoma. It is generally performed in a dark room with dilated pupil. Although doctors can detect a lot of features through this technique, it does not yield a permanent record and has interobserver and intraobserver variabilities. Its sensitivity and specificity has been reported to be only 59% and 73%, respectively.\textsuperscript{7}

A careful examination and detection of change in the optic nerve and the nerve fiber layer is the key to early diagnosis of glaucoma. There are several instruments currently available for imaging of optic nerve and the nerve fiber layer, such as red-free photography, the Topcon ImageNet system, the confocal scanning laser ophthalmoscope, the retinal nerve fiber layer analyzer, and the optical coherence tomograph. The main disadvantages of these techniques however, are the lack of adequate amount of research and high cost.

Another very widely used test for glaucoma is the visual field test. The most common way to measure how well the optic nerve functions is the assessment of the eye's ability to detect the brightness of small points of light both centrally and peripherally. This type of examination is called visual-field testing or perimetry. Although high sensitivity and specificity numbers have been reported for this test,\textsuperscript{5} it depends a lot on the conditions of the test, momentary or immediate state of the patient and the design of the test. Hence they need to be augmented by another screening technique for confirmation.
Chapter 3

Retinal Nerve Fiber Layer and Scanning Laser Polarimetry

The retinal nerve fiber layer is composed of about 1.2-1.5 million ganglion cell axons originating in the retina. The axons are distributed in a characteristic pattern. The axons originating in the region nasal to the optic disc as well as in the macular area run directly toward the optic nerve head, while the axons originating in the temporal section run towards the superior or inferior poles of the optic disc before converging to the nerve head. These fibers are known to be most susceptible to early glaucomatous damage. The peripheral ganglion cell axons travel to the optic nerve head in the peripheral position.
while the central axons take a more superficial path and follow the innermost part within
the optic nerve head. Due to the characteristic pattern of the nerve fiber layer axons, the
thickness of the nerve fiber layer on the vertical poles of the optic disc is much higher
than in the nasal and temporal optic disc poles. The importance of the detection of RNFL
damage as an early sign of glaucoma has been confirmed by numerous studies. Hoyt and
Newman first described it in 198725,26. Histological studies show that as much as 40% of
retinal nerve fiber in the eye can be lost without the detection of characteristic visual
defect in glaucoma patients6. The findings of Sommer and colleagues showed that RNFL
damage could precede visual field loss by up to 5 years27. Hence it is believed that the
detection of damage in nerve fiber layer can lead to an early detection of glaucoma.

RNFL defects related to glaucoma can be either diffused or localized. Localized
defects generally include slit-like or groove-like defects in the RNFL. When these slit
like defects extend to the disc margin or the wedge shaped defects are seen as notches in
the neuroretinal rim in inferior or superior regions, it is judged as a sign of glaucomatous
abnormality. Although localized defects are easier to detect, diffuse RNFL loss is more
common and difficult to diagnose. The second order retinal vessels, which are normally
well concealed by the retinal nerve fiber layer, start to be seen in this kind of defects. The
progressive loss of RNFL thickness in the superior and inferior poles is a sign of
glaucomatous damage.

There are several different techniques for the qualitative examination and
quantitative measurement of nerve fiber damage caused by glaucoma. The qualitative
techniques include examination of the retina through a dilated pupil using an ophthalmoscope or by using a red-free camera or using high-resolution black and white photographs. These are all, however, limited by the pupil size and media optics and tend to have high intra- and interobserver variability. To reduce these difficulties and provide more quantitative measurements of the nerve fiber layer, different devices have been developed. Several instruments have been developed that focus on imaging of the fundus (a mirror-like structure just behind the retina which acts as a light amplifier) and analyzing the topography of the retinal surface\textsuperscript{28,6,7}. These methods attempt to quantify the three-dimensional size and shape of the optic disc, which is considered to represent the bulk of the retinal nerve fibers (Figure 3.1). Stereoscopic fundus photography uses photographs of fundus under different angles to obtain topographic information of the disc. Confocal scanning laser ophthalmoscopy tries to obtain optical section images of the retina by scanning a laser beam across the eye fundus in two dimensions and provides video images on a monitor. These methods include instruments like the Topcon Imagenet, the Rodenstock Optic Nerve Analyzer (Rodenstock Instruments, Munich, Germany) and Heidelberg Retina Tomograph (Heidelberg Engineering, Heidelberg, Germany). Although these methods are a reasonable indicator of the condition of the optic disc, the analysis of the topography of the fundus is an indirect measure of the nerve fiber layer and is only suggestive. Furthermore, the ultimate resolution of these methods is limited by the properties of the ocular media. Hence these kinds of imaging systems are not suitable for accurate measurement of the retinal nerve fiber layer thickness.
Scanning Laser Polarimetry (SLP) is a technique of providing a more quantitative measure of the thickness of the RNFL. The method is based on the principle of using imaging polarimetry to detect the birefringence of the retinal nerve fiber layer\textsuperscript{7,9} (Figure 3.2). This technique utilizes the polarization properties of the retinal nerve fiber layer. The nerve fiber layer and other regions of the retina have been known to have polarization properties or birefringent properties. Form birefringence occurs when a medium consists of parallel cylindrical structure with diameters smaller than the wavelength of light passing through it. A birefringent structure has the ability to change the polarization of a polarized light double passing it\textsuperscript{29}. The ganglion axons that constitute the nerve fiber layer are essentially cylindrical rod-like structures that are parallel to the retinal surface and have extremely small diameters. When a light beam, perpendicular to its surface, is impinged on the retina, the reflected light is split into two rays that travel at different velocities. This is due to the birefringence of the retinal nerve fibers, which being parallel to the retina, are essentially perpendicular to the scanning laser beam. This delay in the two emerging rays or the phase shift between the two is known as the retardation. The amount of retardation is found to be dependent on the
thickness of the RNFL due to its properties and it can be measured using a polarimeter. This retardation (degrees) information is converted to thickness (microns) through the conversion factor based on the histological comparison with monkey eyes.\(^\text{10}\)

![Figure 3.2 Scanning Laser Polarimetry Device - Principle (Courtesy: Laser Diagnostics, San Diego, CA)](image)

The Scanning Laser Polarimeter uses this principle to scan the thickness of the retinal nerve fiber by employing a low power near infrared laser beam to illuminate the human retina. The device using this technology is currently available through Laser Diagnostic Technologies, Inc, San Diego, CA. The device scans the retina with laser beam and measures the retardation at 65,536 discrete points within the retinal area of 15° by 15° in less than 1 second. The software application displays this retardation information on a computer screen as a color-mapped image of the retina (Figure 3.3). A grayscale image of the thickness map of the same retina is also showed in figure 3.4 for reference. The software also provides other software generated information and parameters extracted from the thickness map. The company has generated a normative
database using the thickness maps obtained from variety of patients as well as normal eyes. This is then used to compare the parameters obtained from current patient to provide the probability of the patient having glaucoma based on those parameters. These computer generated parameters include summary measures based on the calculation circle (Figure 3.5).

![Color Coded RNFL thickness map of the 65356 points obtained by the SLP (with the color scale on the right).](image)

**Figure 3.3** Color Coded RNFL thickness map of the 65356 points obtained by the SLP (with the color scale on the right).

Among the number of software-generated parameters provided by the company, the main ones are ‘the number’ and the ‘NFI’ (nerve fiber indicator). The parameter “number” is obtained through a neural network, which is fed with around 100-200 features from the scanned image. The NFI is obtained through a support vector machines recognizer and is available in the newer versions of the device. The latest version of the device implements the correction for the birefringent properties of the parts of the eye other than the nerve fiber layer and is called GDx VCC. Currently doctors use the above-mentioned factors from the device along with other tests and gauge
Figure 3.4 Grayscale representation of the RNFL thickness map image

the disease on subjective basis. Reports have shown that GDx software generated parameters have limited ability for glaucoma detection.\textsuperscript{18-23} One analysis approach proposed a linear discriminant function combining GDx parameters and found better result than the ‘number’\textsuperscript{14}. Several different analyses of the data have been approached and will be discussed briefly.

(a) Norma Glaucom

Fundus Paramete Thickness Deviation TSNIT
To assess the condition of the nerve fiber layer for more analysis, data is extracted from the thickness map by placing a circle at a specified distance around the optic nerve head. The scan image provided by the SLP is divided into four sectors defined as temporal (335°-24°), superior (25°-144°), nasal (145°-214°) and inferior (215°-334°). As shown in figure 3.6, the data from the circled region is taken and plotted to analyze the RNFL thickness. Going from 0° around the circle in the 10-pixel band, the circle is divided into 16, 32 or 64 sectors, and for each sector the thickness values in the band are averaged and taken as a corresponding point value for the graph. This results into the TSNIT graphs shown in figure 3.6. The RNFL around the optic nerve head show a thicker distribution in the superior and inferior regions in a normal eye according to histopathological measurements. When the thickness of the nerve fiber layer around the circle is plotted, a noticeable double-hump pattern is displayed in individuals with normal eyes (Fig. 3.7a).
The double hump pattern found more commonly in non-glaucomatous eyes has humps or high value peaks in the superior and the inferior regions and very low thickness values in the temporal and nasal regions. This can be observed in the graph shown in figure 3.7 which has been obtained from the SLP scan of a non-glaucomatous eye. This double hump pattern is expected to be generally present for eyes without glaucomatous damage since the thickness of the nerve fiber layer has been observed to be higher in superior and inferior regions according to histological studies. Glaucoma leads to loss of nerve fiber layer either in all regions or comparatively more damage in the superior and inferior regions. In the first case the whole TSNIT graph has a general decrease in height or thickness intensity whereas in the other case either higher loss is found in superior or inferior region of the retinal nerve fiber layer or both. Figure 3.7b shows the graph for a glaucomatous eye with more loss in the superior sector as compared to other regions.
The observation of the double-hump pattern in normal eyes and its expected disruption in eyes with glaucoma has lead to more investigation in the analysis of this one dimensional information extracted from the SLP scan data. Various analysis methods have been approached including local measures and more overall shape analysis of the data. The inner bound of the circular band is usually taken around 1.5 – 2.0 times the optic disc diameter from the disc margin. Most of the studies have chosen this ratio for
the inner radius of the band since it has been observed to be the most stable region with regards to the observed graph pattern. Local measures like the correlations of thickness values in superior and inferior sectors, peak-to-trough amplitude in the two humps as well as mean thickness values have been analyzed as parameters\textsuperscript{20}. Other techniques based on local measures like relative surface height\textsuperscript{17}, and sectoral-based analysis\textsuperscript{18} have also been reported with better results than GDx parameters. Another approach proposed discriminant analysis of 30\textsuperscript{0} sectoral data from the scanning laser polarimetry\textsuperscript{16}.

Some other techniques are based on a global shape analysis of the double-hump pattern and have proved to be more robust. One approach for the analysis of the double-hump pattern is to describe it using Fourier analysis. Several studies have been made using Fourier analysis, using either single Fourier coefficients to differentiate/detect glaucoma or various combinations\textsuperscript{21, 22}. The sensitivity and specificity of these methods were around 96\% and 90\% respectively and show that they are more robust and can lead to better discrimination than the GDx parameters as well as other local measures and statistical analysis. Another shape analysis technique recently proposed by Essock et. al.\textsuperscript{23} was to use the combination of Fourier and wavelet analysis. The Fourier analysis was to analyze the global shape of the double-hump pattern while the wavelet analysis concentrates on analyzing the more local structure of the TSNIT graph. This approach has also shown improvements over the local measures and GDx parameters with sensitivity and specificity of 96.5\% and 94.1\% respectively.
All these techniques are an improvement in general to the machine generated parameters or the ‘number’ alone. These techniques however use only a part of the two dimensional data obtained from scanning the entire 15° area of the retina. Thus around 75-80% of the data in the SLP scan image is never really used for analysis and detection of the disease. The center of the optic disc and its radius are determined manually by a technician or an observing ophthalmologist and is thus subjective. The data obtained from the circular band, although has been observed to be stable in that region is still subjective to the correct determination of the center and radius of the disc. All these factors lead to a need for more analysis of the image as a whole and to extract features that are derived by using more information rather than limiting it to one part of the image.
Chapter 4

Analysis of Scanning Laser Polarimetry Image

This thesis presents a unique approach to the analysis of data from scanning laser polarimetry devices. The first phase of the thesis was mainly to focus on generation and selection of some useful features through experimentation on available data. The first requirement of this phase was to procure images of scan data from a Scanning Laser Polarimetry device for both normal or non-glaucomatous eyes as well as scan data from glaucoma patients. The data for initial analysis and derivation need not be a very big set of images. Dr. Michael Sinai, PhD, Director of Clinical Research, Laser Diagnostic, (San
Diego) was kind enough to share around 10 images of each case along with other analysis information that the SLP machine calculates, from his previous experiments. The company’s latest machine, GDx VCC was used to obtain these scans. VCC stand for Variable Corneal Compensation. Studies show that other regions of the eye, like the cornea and crystalline lens also possess some birefringent properties. Since this will affect the scan data by adding to the RNFL thickness calculation according to the thickness of those structures, this affects the accuracy of the scanned thickness map. An anterior segment compensator assumes a fixed slow axis of corneal birefringence and it aligns its axis with the corneal polarization axis to cancel the effect of corneal birefringence without affecting RNFL polarization\textsuperscript{31}. The GDx VCC is a scanning laser polarimeter, which employs the compensation technique to take care of the birefringent properties of other parts of the ocular region scanned by the laser beam. Thus the GDx VCC was a better choice to obtain the data than the previous devices by the company\textsuperscript{32,33}.

The common approach to the feature extraction on these scans until now has been to use the 32 or 64-point data from the circular band around the center of the disc at about 1.75 disc diameter. The techniques used currently for the analysis of the scan data from the Scanning laser polarimetry devices have chiefly depended on this ring data around the optic disc center. Since a doctor or technician manually determines the center and radius of this ring, it is subjective and this can lead to variability into the extracted data. And although these data provide considerable amount of information for glaucoma recognition, the information in the rest of the scanned data must not be completely neglected. So the next step after obtaining the sample images for both the cases was to
experiment with these images and to figure out acceptable and useful features that could help improve on the analysis of the scans for detection of glaucoma.

The images used are a general size of 128 X 256. The data of the entire image is used and hence the final classification is not to be affected by the location of the center of the optic disc in the image. It was observed that the retinal scan has a butterfly pattern (Fig.4.1) and hence it gives rise to the double-hump pattern of the TSNIT graphs. Hence various projections of the image were taken assuming that some useful information can be extracted from it. The general idea is to base the obtained one dimensional data on the whole region covered by the retinal nerve fiber layers instead of on the circular band region and at the same time eliminate the necessity to calculate the center or radius of the optic disc. The projections taken were: $0^\circ$, $90^\circ$, $25^\circ$, $45^\circ$, $145^\circ$ and $135^\circ$. However, as expected not all projections were as helpful in providing distinguishing features. However, the $90^\circ$ projection or vertical profile of the image showed very distinct characteristics in both groups. The vertical profile of the “normal” images was found to have a double-hump pattern quite similar to that of the ring data as opposed to the glaucomatous profiles, which lacked any such pattern.
Although the horizontal profile (128 data points) was in itself not very useful as a feature vector, the global shape measure of the profile could be used to emphasize characteristics that typify the shape of the variation of the thickness level in the profile.

Fourier analysis can provide such a measure and hence has been used on the horizontal profiles. Since the double hump pattern in the normal scans has a somewhat sinusoidal shape (with about one cycle), the criteria for detecting glaucoma can be developed based on the amplitudes of the frequency components. Fourier analysis is a technique to decompose a given signal and represent it by a set of harmonically related sine and cosine waves with different frequencies, amplitudes and phases – harmonics. The result of Fourier analysis is a set of coefficients corresponding to different frequencies and it represents the amount of sine and cosine signal of that frequency present in the given signal. Thus the coefficients have a physical meaning in frequency domain that can be correlated to the spatial domain. And hence this can be used as a feature vector in the pattern recognition system. This feature vector is first passed through principal component analysis to reduce the size of the feature vector and then the discrimination of the samples into the two classes is performed using Fisher’s Linear Discriminant.
A more detailed analysis of the vertical profile or the $90^\circ$ projection is to perform a wavelet transform of the data along with the Fourier analysis. The wavelet transform is a relatively new concept, however, quite some literature can be found in various articles and books\textsuperscript{11,34-36}. Just like in the Fourier transform, the signal of a continuous variable is mapped into a sequence of coefficients. Wavelet analysis is based on a decomposition of a signal using typically (not necessarily) an orthonormal family of basis functions. The basis function used for wavelet analysis is called the ‘wavelet’, which, unlike a sinusoid, is localized in time and space. It is therefore well suited for analysis of transient, time-varying signals and good in detecting discontinuities or abrupt changes in signals. The signal is multiplied with a function (wavelet) and the transform is computed separately for different segments of time-domain signal. The transformed signal is a function of two variables, the translation and scale parameters, and the transforming function is called the

\textbf{Fig. 4.3} Wavelet analysis of the Vertical profile of a Normal scan (only second level detail coefficients shown here)
mother wavelet. If \( f(t) \) is a square integrable function, then the discrete wavelet transform (DWT) pair of the function with respect to a wavelet \( \psi(t) \) and the scaling function \( \phi(t) \) is defined as

\[
W_\phi (j, k) = \frac{1}{\sqrt{M}} \sum_x f(x) \phi_{j_0,k}(x)
\]

(1)

\[
W_\psi (j, k) = \frac{1}{\sqrt{M}} \sum_x f(x) \psi_{j,k}(x), \text{ for } j \geq j_0;
\]

(2)

and

\[
f(x) = \frac{1}{\sqrt{M}} \sum_k W_\phi (j_0,k) \phi_{j_0,k}(x) + \frac{1}{\sqrt{M}} \sum_{j=j_0}^{J-1} \sum_k W_\psi (j,k) \psi_{j,k}(x)
\]

(3)

where \( f(x), \phi(t), \) and \( \psi(t) \) are functions of the discrete variable \( x = 0,1,2,...,M-1; \) and \( M \) is selected to be a power of 2 (i.e. \( M = 2^J \)) so that the summations are performed over \( j = 0,1,...,J-1 \) and \( k = 0,1,...,2^J-1. \) Hence the transform consists of \( M \) coefficients, and scales from 0 to \( J-1. \) The process of computing the wavelet coefficients is called signal decomposition and the coefficients thus obtained by above equations are called approximation (Eq. 1) and detail (Eq. 2) respectively. The above equations are valid for orthonormal basis and tight frames only\(^{35}\). Figures 4.3 and 4.4 show the wavelet analysis of the normal and the glaucoma scan vertical profiles respectively. The figures only show a first level decomposition with the signal (top), its approximate coefficients (bottom left) that are the average low-frequency part of the signal and define the overall shape of the signal and its detail coefficients (bottom right) that represent the small changes in the signal.
In order to reflect small changes in the signal structure that may be lost by the Fourier analysis, a 2nd level wavelet transform was performed using an 8th-order wavelet named “Symmlets”, along with the Fourier analysis of the profile. The vertical profile was decomposed using wavelet analysis (M = 128) and the detail coefficients from the second level (32 points) were used and combined with the Fourier transform of the average coefficients after normalizing (to range [0,1]) as a feature set.

Fig. 4.4 Wavelet analysis of the Vertical profile of Glaucoma scan (only second level detail coefficients shown here)
The Fourier analysis of the entire scan image provides as well some useful features due to the butterfly pattern from the center of the optic disc. In order to capture the pattern of the entire scan data, the two-dimensional Fourier Transforms (FT) of the images was taken. The 2D Fourier transform of the “normal” scans (Fig. 4.5b) were observed to have several ‘spike’ like streaks coming out in various directions from the center, as opposed to an almost even spread center region in the Fourier transform of the “glaucoma” (Fig. 4.5a) scans. This is believed to be a direct result of the butterfly pattern in the original scans. Hence features can be drawn out to define the spike pattern in the Fourier transform. For this purpose, a circular ring band at an inner radius of 20 pixels and width of 10 pixels band was extracted. 64-point data were obtained from this circular ring band around the center of the two-dimensional Fourier transform. Since the Fourier transform is symmetric only one quarter of the points drawn out from the circular band needs to be used.

**Fig 4.6** Average image of the a) “Glaucomatous” and b) “Normal ” scans
The image of the scans can be assumed to have properties, which are common to each group but cannot be separately obtained. For such characteristics the average image of each group can be used as a base image (Fig. 4.6) and a pattern-image (Fig. 4.7) for each group can be derived. The average scans were obtained by manually finding the center of each image and a simple average of all the images belonging to each group. Since the average images were not directly used either for deriving the pattern image or to find the correlation coefficient, no extra steps were taken for more registration of the images. As seen in the averages scans, the normal scan has high intensity in the center region with a X shape as compared to the other parts of the scan while the intensity changes in the average glaucoma scan is more subdued and spread out. So a pattern image was generated for the normal group (Fig. 4.7) was found to be useful to find the correlation of each data image with the pattern image and use it as one of the features. Since the scans of right and left eye had slight differences that were observed in the general shape of the pattern, two different pattern images were used for the left and right eyes. The correlation values gave a desirable separation between the two classes; hence this has been used as a distinguishing feature for the detection system.
The set of features discussed above were first used separately and passed through the PCA analysis and lastly through the Fisher's Linear Discriminant analysis (except the correlation feature that was already a single dimension feature). These were then evaluated separately as features for the classification system through the ROC analysis. In addition, all the features were normalized and put together in a single feature vector to form the final classification system. This was also evaluated using ROC. For comparison purposes, the Fourier analysis of the 64-point data obtained from the ring in original scan at around 1.75 times the disc center was also performed. The results of this have also been evaluated for the same sample set using the ROC curve and presented in the sixth chapter.
Chapter 5

Feature Optimization And Classification

The classification features now been recognized, the next step of the classification process will be to optimize the feature vector set and reduce its dimensionality without losing feature variability in order to perform the classification. This chapter explains the theory of the steps used for feature optimization and the method employed for performing the classification.
**Feature Optimization:**

The main objective of this step in the classification process is to reduce the dimension of the feature vector without losing the variability of the feature set. Principal Component analysis (PCA) identifies linear combinations of the feature set so that most of the variability (information) of the original feature set is contained within that combination\textsuperscript{11,12,37}. It essentially transforms a feature vector with correlated variables into a smaller sized feature vector with uncorrelated variables. These uncorrelated variables are called the principal components. The first principal component is the projection of the data points (points in the feature set/feature vector) in the direction of the line giving the best orthogonal regression fit to the data points. Since the best fit to this type should pass through the mean, the data points are centered on the mean by subtracting the mean from the data points. The first principal component is hence the projection of the data points into the direction with maximal variance of the projected points. The first principal component corresponds to the maximum variability of the original feature set and the second component corresponds to the second highest variability of the set and so forth, there are \( p \) principal components (\( p \) is the feature vector size).

The first step in the PCA is to find the sample covariance matrix \( S \), for the combined samples of both classes. Then the eigenvalues and corresponding eigenvectors of this matrix are calculated. The combination of the feature points that has the maximum variability is obtained in the direction of the first principal component and this direction is that of the eigenvector corresponding to the highest eigenvalues. Hence the eigenvalues are ordered from highest to lowest and the accordingly ordered eigenvectors represent the
principal component directions. A matrix $A$ is calculated by using the ordered eigenvectors of the covariance matrix of the feature vectors. The transformation matrix is then extracted from $A$ by taking the eigenvectors corresponding to only the $k$ largest eigenvalues. The new transformation matrix $A_k$ is then used to derive the new compressed feature vector of dimension $k$.

**Classification:**

The compressed feature vectors obtained in the last step are now passed through a classification process that decides whether the feature vector belongs to “normal” group or “glaucomatous” group. The classifier predicts the membership of each sample in the data set based on its feature vector. In a linear discriminant analysis (LDF) \cite{11, 12, 37}, a linear combination of the feature vector variables is fed to the classifier to predict group membership. First a trainee set is used where the feature vector and the group membership are known. This is then used to form a model that can be used as the classifier. The Fisher’s LDF has been used as a classifier for its simplicity and robustness.

The optimized feature set obtained from the PCA analysis is separated randomly and uniformly into two sets – Trainee and Test. The current data set consisted of 92 images of each group. Each of the groups was divided into two sets of 46 samples by randomly selecting these samples. The trainee set is used to formulate the model for the LDF and the test set is used to assess the predictability and reliability of the model formulated. The first step in formulating the model is to find the sample mean of both groups ($Mean_{\text{Group1}}$, $Mean_{\text{Group2}}$) as well as the combined averaged for both the
groups \((\text{Sample\_Mean})\). This will generate three different average vectors that are then used to find the between-groups and within-group variability. If the \(p\) dimensional sample feature vector sets corresponding to the two classes are described by the \(x_{i1}\) and \(x_{i2}\), then the sample mean vectors are defined by

\[
\bar{x}_i = \frac{1}{n_i} \sum_{j=1}^{n_i} x_{ij} \quad i = 1,2
\]

and the overall mean vector is defined as

\[
\bar{x} = \frac{\sum_{i=1}^{2} n_i \bar{x}_i}{\sum_{i=1}^{2} n_i}
\]

Thus the overall mean \((\text{Sample\_Mean})\) is taken as the weighted average of the samples since it is weighted by \(n_i\) which is the number of samples in the corresponding \(i\)th trainee group set. Next, the between-groups variability matrix \(B\) is defined as

\[
B = \sum_{i=1}^{2} n_i (\bar{x}_i - \bar{x})(\bar{x}_i - \bar{x})^T
\]

and the within-group variability matrix \(W\) is defined as

\[
W = \sum_{i=1}^{2} (n_i - 1) \sum_{i=1}^{2} n_i (\bar{x}_{ij} - \bar{x})(\bar{x}_{ij} - \bar{x})^T
\]

The Fisher’s LDF is based on the idea to find a coefficient vector \(a\) that maximizes separation of the samples while making the classification of the groups a linear process. Hence in order to find a vector \(a\), such that it maximizes \(\frac{a^T B a}{a^T W a}\), the eigenvalues and eigenvectors of the matrix \(W^{-1} B\) are calculated and the eigenvector corresponding to the highest eigenvalues is the vector \(a\). To obtain the single dimensional value from the feature vector \(x\), the combination \(a x\) is used and is called the first discriminant. Thus the \(k\)
dimensional feature vector obtained from the PCA analysis is converted to a single dimension using the Fisher’s LDF and then using a single threshold (linear discriminant), the sample data can be divided into two separate groups.

This concludes the steps in classification of the given sample set into the two classes of the ‘normal’ and the ‘glaucoma’ cases. To assess the classification method and the features used, the Receiver Operating Characteristics (ROC) analysis is performed on the results obtained. The next chapter shows the result of the methods used and interprets the performance of the given classification system using the ROC curve.
Chapter 6

Experimental results & Discussion

Our present sample consists of SLP scans of 92 glaucomatous eyes and 92 normal eyes, obtained from 47 glaucoma patients and 45 healthy people. Dr. Michael Sinai of Laser Diagnostics made the data set and its diagnosis (classification based on clinical findings) available to us for research purposes. This set was divided randomly and uniformly into two subsets. One subset was used as a trainee set for the classifier while the other was used as a test set. After the classification results were obtained, the ROC
analysis for performance evaluation was done and its theory is explained briefly in the next section.

**Receiver Operating Characteristic (ROC) curve:**

To evaluate the performance of the classification system formed by using the derived features, an ROC curve analysis has been employed. Receiver Operating Characteristic (ROC) analysis is a procedure used in medical applications to evaluate the accuracy of diagnostic techniques. This is a simple procedure to test the overlap between the distributions of the two classes and can be used to evaluate the discriminatory performance of any quantitative diagnostic test. The ROC curve can be constructed by sweeping the threshold and computing percentages of wrong and correct classifications over the available training feature vectors. This analysis comes typically after the classification of the samples has been done using the technique to be evaluated. Using some “gold standard” to decide who actually has the disease (i.e. which data sample actually belongs to a glaucoma patient) the results are recorded as the truth basis for the classification comparison. The “gold standard” or truth basis used in this experiment was the diagnosis provided on the chart sheet with the images by Dr. Sinai. The images/ GDx-VCC scans that were collected were marked as glaucomatous or normal based on the diagnosis by doctors using the obtained medical history, ophthalmic exam, refraction and visual acuity, biomicroscopy, IOP measurements, optic disc photography and automated perimetry. The detailed information of this procedure can be
obtained from the company records upon request but is outside the scope of this thesis to be attached as a proof.

Once the truth basis or the “gold standard” results are available and the results for the same set of samples are generated using the classification system to be evaluated, the ROC curve can be generated. To plot the ROC curve, the True positive and the False Positive fractions must be calculated. The True Positive fraction represents the number of samples that have been selected to be in class ‘glaucomatous’ and actually belong to a glaucoma patient. This is also called the sensitivity of the classification system. Similarly the False Positive fraction is the number of samples that were classified as ‘normal’ but actually belong to eyes of glaucoma patients according to the “gold standard”. The True Negative fraction is the number of samples that were correctly classified to be ‘normal’ and is also called the Specificity of the classification system. The Sensitivity is how good the classification system is at picking out the patients with glaucoma and the Specificity is the ability of the system to pick out patients who do not have the disease. The ROC curve is simply an exploration of what happens to the True Positive fraction (sensitivity) and False Positive fraction (1-specificity) as we vary the threshold of the linear classifier from one end of the data values spread to the other. Hence the ROC is a plot of the sensitivity vs. (1-specificity) while varying the discriminant threshold value. A measure that is generally used to evaluate the performance through the ROC curve is the area under the curve. A value of 0.5 represents that the system is as good as ‘flipping a coin’, meaning that the chance of any particular classification being right is 50%. A value of 1 for the area signifies that the classification is undoubtedly always true and the
classification of any sample has 100% chance of being true. Thus the closer the value of area is to 1, the better classifier performance. In addition to this value, the best values of sensitivity for corresponding specificity are also observed from the ROC curve and noted to show the performance of the classifier.

**Classification techniques (using different feature sets) and ROC curves:**

**Feature Set 1 - Fourier transform of vertical profile of the scans:**

The first feature set that was analyzed was the Fourier transform of the vertical profile or the $90^\circ$ projection of the eye scans. The profile was taken by taking the average of the image along the horizontal axis. However, the feature set may not necessarily be derived separately from the 2D Fourier transform, since, the Fourier slice theorem states that the one-dimensional Fourier transform of the vertical projection data is just a slice of the two-dimensional Fourier transform (2D-FT) of the scan. Therefore the 2D FT that is already being used for deriving another feature set (ring data – set 3) can also be used to extract this feature set. Since the Fourier transform is symmetric, only 64 points from this feature vector were used. This 64-point feature vector was used to obtain the reduced feature vector through the principal component analysis (as explained in Chapter 5). Since 97.18% of the variability of the data set was contained in the first 15 components, only those components corresponding to the highest 15 eigenvalues have been used. Thus the new feature vector was reduced from 64-point to a 15-point feature vector. This 15-point vector was used as the final optimized vector for the Fisher’s LDF analysis (as explained in Chapter 5). The linear discriminant analysis projects the given
multidimensional feature vector into a single dimension while maximizing the group variability. The results of the discriminant analysis showed sensitivity and specificity of 75.12% and 99.15% respectively. The receiver-operating curve (ROC) for this feature is as shown in Fig. 6.1 and the area under the curve is 0.7789.

**Feature Set 2: Wavelet analysis of the vertical profile of scans**

The next feature vector to be analyzed was the detail coefficients from the second level (32 points) of the wavelet analysis of the vertical profile, combined with the Fourier transform of the approximation coefficients. Since two different sets of values are being combined here, the values of each were normalized to the range of [0,1] before performing the PCA and classification. The first 10 principal components contained 89.29% of the variability and hence were enough to be used as the LDF input. The area under the curve was found to increase to 0.8235, however the sensitivity was only found to be 58.7% for specificity of 89%.

![Figure 6.1 ROC curve for Fourier analysis of 90° projection](image)
Feature Set 3: Ring data from two-dimensional FT of the scans

The next feature vector set that was obtained from the two-dimensional Fourier transform of the eye scans. Since the Fourier transform is symmetric, the ring data was obtained from one-quarter sector around the center of the 2D Fourier transform matrix. After this feature was passed through the principal component analysis, since 94.63% of the variability of the data set was contained in the first 10 components, therefore only those components corresponding to the highest 10 eigenvalues have been used. Thus the new feature vector was reduced from 32-point to a 10-point feature vector. This 10-point vector was used as the final optimized vector for the Fisher’s LDF analysis. The receiver-operating curve (ROC) for this feature is as shown in Fig. 6.3. The area under the curve is 0.7813. The results of the discriminant analysis showed sensitivity and specificity of 74.92% and 91.5% respectively.

Figure 6.2 ROC curve for Wavelet - Fourier analysis of 90° projection
Feature Set 4: Ring data from two-dimensional FT of the scans

The fourth feature set simply consisted of a single feature, the correlation coefficient of the scan images with the generated pattern image. The ROC curve for this feature is shown in figure 6.4 and has an area under the curve of 0.8287 with sensitivity and specificity of 67.5% and 82% respectively.

Figure 6.4 ROC curve for Correlation coefficient

In the last step for building the classification system, all the features were normalized to a range of [0,1] and combined as a single feature set. The final feature set
thus consisted of the 64 point FT of the projection of the scan data, 32 point second level
detail coefficients from the wavelet transform, 32-point ring data from the 2D FT of the
scan as well as the correlation coefficient, thus making it a 128-point feature vector. The
first 15 principal components were found to contain about 98% of the variability and
hence were used for the LDF. The results of the LDF analysis using a uniform and
random division of the data set showed comparable results to the existing techniques that
are under study for the analysis of the GDx-VCC scans. The ROC curve for the entire
feature set is shown in figure 6.5. The area under the curve is 0.8433 with sensitivity and
specificity of 84.68% and 91.3% respectively.

In order to compare the current work with one of the recent techniques applied for
analysis of the scan data, a Fourier analysis of the ring data from scan was also performed
on the same data set. 64-point data (TSNIT graph) was extracted by taking a ring of
radius at about 20-pixel from the center and width of around 10 pixel from the scans. The
Fourier transform was applied to these data and the 32-point coefficients were fed to the
PCA analysis and the LDF classification. The ROC curve for this feature set is shown in
figure 6.6 and its area under the curve was found to be 0.8566 and sensitivity and specificity values of 76.79% and 91.3% respectively.

**Figure 6.6** ROC curve for FT of TSNIT graph

**Figure 6.7** ROC curves for
(red) Combination of all current features
(blue) FT of TSNIT graph
A comparison of the ROC curves for both the classification systems can be seen in figure 6.7. Table 6.1 shows the comparisons of the area under the curve, sensitivity and specificity values for all the different feature sets used, the final combination of all the proposed features into one feature set as well as the Fourier analysis of the TSNIT graph.

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Area under ROC curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT of 90° projection</td>
<td>75.12%</td>
<td>99.15%</td>
<td>0.7789</td>
</tr>
<tr>
<td>Wavelet analysis with FT of 90° projection</td>
<td>58.7%</td>
<td>89%</td>
<td>0.8235</td>
</tr>
<tr>
<td>Ring data from 2D FT</td>
<td>74.92%</td>
<td>91.5%</td>
<td>0.7813</td>
</tr>
<tr>
<td>Correlation coefficient with pattern image</td>
<td>67.5%</td>
<td>82%</td>
<td>0.8287</td>
</tr>
<tr>
<td>Combined Feature set</td>
<td>84.78%</td>
<td>91.3%</td>
<td>0.8433</td>
</tr>
<tr>
<td>FFTA – based on previously performed analysis</td>
<td>76.09%</td>
<td>91.3%</td>
<td>0.8588</td>
</tr>
</tbody>
</table>

*Table 6.1* Performance evaluation of the different feature sets based on the ROC analysis using the same trainee and test set, chosen randomly and uniformly.
Chapter 7

**Conclusion**

Various investigators have applied different tools for analysis of the scanning laser polarimetry data to classify glaucomatous eyes from normal. In this thesis, new approaches of extracting features from the clinical scans have been proposed and used for classification. Projection data reflect the information over a major portion of the butterfly pattern of the scan in the spatial domain. The two-dimensional Fourier transform is a global transformation; therefore values at each pixel location in the Fourier domain carry some information about the overall scan pattern in the spatial domain. Furthermore, we know from Fourier slice theorem\(^{35}\) that the one-dimensional Fourier transform of the
vertical projection data is just a horizontal slice of the two-dimensional Fourier transform (2D-FT) of the scan. Therefore the two methods using the Fourier analysis amount to extracting two subsets of information from the 2D-FT. One is a vertical slice of 2D-FT and the other over a ring in the 2D-FT. Both have been seen to be useful for classification. Although the area under the curve obtained for these features was not as good as the other feature sets, the best sensitivity obtained for high specificity showed significant prospect of its use in aiding the classification process. The wavelet analysis in addition to the Fourier analysis of the projection data was found to give a high area under the curve, although failing to produce respective high sensitivity for required specificity. Nevertheless, the feature provides high separability and hence was added to the feature set for the final classification. The pattern image used for correlation coefficient feature has proved to capture most of the pattern found in the normal scans vs. the glaucoma scans and has given comparable results to the previous work by just using the single feature. More pattern images to capture thoroughly the differences in the scan patterns are proposed for future work.

The combined feature set derived from all the obtained features had given an area under the curve comparable (although not higher) to the existing Fourier analysis of TSNIT graph technique, (0.8433) and has shown higher sensitivity (82.68%) for the same specificity values and the same data set. Hence more research into these features is proposed in order to combine the existing techniques, which definitely had a better ROC area with the current features for more accuracy and sensitivity of the classification system.
The progressive nature of nerve damage and the changes that it may produce in the RNFL scans is complex and not yet fully understood. It is quite possible that diagnostic features extracted from existing methods may not be sensitive to the overall changes in the scan pattern. Since the Fourier domain approach allows us to pick features that depend on the overall pattern, and the pattern image correlation help in bringing out the class-specific pattern in the scans, it is believed that this feature set would be able to detect progressive changes and quantify it for differential diagnosis. Future work to test this hypothesis is proposed. I conclude that my approach offers an effective tool for enhancing diagnostic abilities and can add to the sensitivity of the existing techniques to improve performance.
References


18. FA Medeiros, R Susanna(Jr.), Comparison of algorithms for detection of localized nerve fiber defects using scanning laser polarimetry, Br J Ophthalmology, 2003; 87:413-419


The thickness image map for each eye was available in a company specific file format, (.MIF) that stored both the fundus photographic image and the thickness map in a single file. Dr. Michael Sinai generously provided this function for reading the thickness map from the files along with the files for the 192 eye scans.

```matlab
function [Fundus, Thickness] = OpenLDTMIF(FileNum,Path)

 numFrames = 2;
 Image_Slices = numFrames;
 Header = 214;
 SubHeader = 98;
 ImageWdth = 256;
```

Appendix
ImageHght = 128;
FileLength = ImageHght * ImageWdth;

filename = [ int2str(FileNum) '.MIF'];
VCSELPATH = Path;

if length(filename) ~= 0
    [path, name, ext, ver] = fileparts( filename );
    [file, message] = fopen([VCSELPATH, filename], 'r', 'l');
    filename = cat(2, name, ext);
else
    outer = 0;
    return
end

if file == -1
    a = ['file ', filename, ' ERROR.'];
    error(a);
end

% Set array dimensions.
out = zeros(ImageWdth, ImageHght, Image_Slices);
% Read in image file.
for i = 1 : Image_Slices
    fseek( file, (Header+i*SubHeader+(i-1)*FileLength), -1 );  % next slice position
    out(:, :, i) = fread(file, [ImageWdth ImageHght], 'uint8');
end
fclose(file);

Fundus = out(:,:,1)';
Thickness = out(:,:,2)'*0.78125;
return;

%%The thickness maps read from .MIF files were saved in a .mat format for easy access.

PathN = ['C:\MATLAB6p5\work\'];
PathG = ['C:\MATLAB6p5\work\'];

%%number of samples in each group
NumSamples = 92;

for i = 1 : NumSamples
    FileNum = i;
    [FundusN ThicknessN] = OpenLDTMIF(FileNum,PathN);
    %normal thickness map in NT and fundus images in NF
    NT(:,:,i) = ThicknessN;
    NF(:,:,i) = FundusN;
    [FundusG ThicknessG] = OpenLDTMIF(FileNum,PathG);
    %normal thickness map in NT and fundus images in NF

63
GT(:,:,i) = ThicknessG;
GF(:,:,i) = FundusG;
end

save C:\MATLAB6p5\work\Nfiles.mat NT
save C:\MATLAB6p5\work\Gfiles.mat GT
save C:\MATLAB6p5\work\NFundus.mat NF
save C:\MATLAB6p5\work\GFundus.mat GF

% Finding all the features

%% Feature Set 1 – Fourier Transform of vertical profile

for i = 1 : NumSamples

%% taking the 90° projection of the scan and normalizing them from 0-1
VP_G(i,:) = mean(GT(:,:,i));
VP_G(i,:) = (VP_G(i,:) - min(VP_G(i,:))) / (max(max(VP_G(i,:))) - min(VP_G(i,:)));
VP_N(i,:) = mean(NF(:,i));
VP_N(i,:) = (VP_N(i,:) - min(VP_N(i,:))) / (max(max(VP_N(i,:))) - min(VP_N(i,:)));

%% Taking Fourier Transform of profile
TempG = abs(log(fftshift(fft(VP_G(i,:)))));
FT_VP_G(i,:) = TempG(66:96);
TempN = abs(log(fftshift(fft(VP_N(i,:)))));
FT_VP_N(i,:) = TempN(66:96);
end

%% Feature Set 2 – Wavelet-Fourier Transform of vertical profile

%% wavelet decomposition – 2nd level
[CN,LN] = wavedec(VP_N(i,:),2,'sym8');
[CG,LG] = wavedec(VP_G(i,:),2,'sym8');

%% saving the approximate coefficients and the detail coefficients and normalizing
VN(i,:) = appcoef(CN,LN,'sym8',2);
WN(i,:) = detcoef(CN,LN,2);
WN(i,:) = (WN(i,:) - min(WN(i,:))) / (max(WN(i,:)) - min(WN(i,:)));

VG(i,:) = appcoef(CG,LG,'sym8',2);
WG(i,:) = detcoef(CG,LG,2);
WG(i,:) = (WG(i,:) - min(WG(i,:))) / (max(WG(i,:)) - min(WG(i,:)));

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Feature Set 3 – Correlation Coefficient – with pattern image

pattern images – for right and left eye
AvgR_N
AvgL_N

finding correlation coefficient – left and right eyes were stored alternatively
CG(a) = corr2(GT(:,:,a),AvgR_N);
CG(a+1) = corr2(GT(:,:,a+1),AvgL_N);
CN(a) = corr2(NT(:,:,a),AvgR_N);
CN(a+1) = corr2(NT(:,:,a+1),AvgL_N);

Feature Set 4 – 2D Fourier Transform- ring data obtained

finding 2D fft
RingDataG(:,:,i) = abs(log(fftshift(fft2(GT(:,:,i)))));
RingDataN(:,:,i) = abs(log(fftshift(fft2(NT(:,:,i)))));

extracting ring data
InnerRadius = 20;
OuterRadius = 30;
Radius = [InnerRadius OuterRadius];
DataPoints = 32;
RingDataG(:,:,i) = RingDataG(:,:,i) ./ max(max(RingDataG(:,:,i)));
RingDataG_FT(i,:) = RingData(abs(RingDataG(:,:,i)),Radius,DataPoints);
RingDataN(:,:,i) = RingDataN(:,:,i) ./ max(max(RingDataN(:,:,i)));
RingDataN_FT(i,:) = RingData(abs(RingDataN(:,:,i)),Radius,DataPoints);

function X = RingData(I,radius,datapts)

[m n] = size(I);
center_x = m/2;
center_y = n/2;
Rpoints = 1;
for k = 1 : datapts
    X(k) = 0;
    for phi = (180/datapts)*(k-1) + 180 : (180/datapts)*k + 180
        for r = radius(1) : Rpoints : radius(2)
            x(k) = center_x + round( r * cos(phi*pi/180) );
            y(k) = center_y + round( r * sin(phi*pi/180) );
            X(k) = X(k) + I(x(k),y(k));
        end
    end
end
end
Principal component analysis of the feature vectors that need to be reduced

\[ X = \text{GlaucomaSampleFeatureVector} ; \]
\[ Y = \_\text{NormalSampleFeatureVector}; \]
\[ \text{Samples} = [X;Y]; \]
\[ [n,m] = \text{size(Samples)}; \]

%% Finding the Standard Deviation and Mean of each coloum
\[ \text{Std\_Samples} = \text{repmat(\text{std(Samples)},[n,1])}; \]
\[ \text{MeanSamples} = \text{repmat(\text{mean(Samples)},[n,1])}; \]

%% Standardizing by subtracting the mean and dividing by
%% the standard deviation
\[ \text{FeatVect} = (\text{Samples} - \text{MeanSamples})/\text{Std\_Samples}; \]
\[ \text{FinalFeat} = \text{FeatVect}; \]

%% princomp is a matlab command to do the PCA analysis
\[ [\text{PC}, \text{SCORE}, \text{LATENT}, \text{TSQUARE}] = \text{princomp(FinalFeat)}; \]

%% k - decided based on what value of variability is acceptable – must be > 80%
\[ \text{Total\_Variability} = \text{sum(Proportion(1:k))} * 100 \]

\[ \text{EigVect} = \text{PC}(1:k,:); \]
\[ \text{PCA\_ft\_hp} = \text{SCORE}(:,1:8); \]

\[ \text{sumEigVal} = \text{sum((LATENT))}; \]
\[ \text{Proportion} = ((\text{LATENT}))/\text{sumEigVal}; \]

Fisher’s Linear Discriminant Function for dividing the data into two groups

\[ \text{NumSamplesG} = 92; \] \% Total number of samples of Glaucoma(Grp 1)
\[ \text{NumSamplesN} = 92; \] \% Total number of samples of Normal(Grp 2)
\[ \text{RandOrderG} = \text{randperm(NumSamplesG)}; \] \% taking a random order for the samples
\[ \text{SzTraineeG} = 46 \] \% Taking a size for trainee set of Group 1
\[ \text{SzTestG} = \text{NumSamplesG} - \text{SzTraineeG}; \] \% Size of test set of Group 1
\[ \text{RandOrderN} = \text{randperm(NumSamplesN)}; \] \% Taking a random order for the samples
\[ \text{SzTraineeN} = 46 \] \% Taking a size for trainee set of Group 2
\[ \text{SzTestN} = \text{NumSamplesN} - \text{SzTraineeN}; \] \% Size of test set of Group 2

\[ \text{PCA\_G} = \text{PCA\_ringdata(1:92,:)}; \]
\[ \text{PCA\_N} = \text{PCA\_ringdata(93:184,:)}; \]
Setting the Trainee and Test sets for both groups:

\[ \text{TraineeG} = \text{RandOrderG}(1: \text{SzTraineeG}); \]
\[ \text{TraineeN} = \text{RandOrderN}(1: \text{SzTraineeN}); \]
\[ n(1) = \text{length(TraineeG)}; \]
\[ n(2) = \text{length(TraineeN)}; \]
\[ N = \text{sum(n)}; \]
\[ \text{TestG} = \text{RandOrderG}(\text{SzTraineeG}+1: \text{NumSamplesG}); \]
\[ \text{TestN} = \text{RandOrderN}(\text{SzTraineeN}+1: \text{NumSamplesN}); \]

Extracting the features from the trainee set and combining them onto a single feature vector:

\[ \text{Group1Trainee} = \text{PCA}_G(\text{TraineeG},:)' \]
\[ \text{Group2Trainee} = \text{PCA}_N(\text{TraineeN},:)'; \]

Finding the sample Mean of each class:

\[ \text{SampleMeanGroup1} = \text{mean(Group1Trainee,2)}; \]
\[ \text{SampleMeanGroup2} = \text{mean(Group2Trainee,2)}; \]

Finding the Overall Mean:

\[ \text{OverallMean} = (n(1) * \text{SampleMeanGroup1} + n(2) * \text{SampleMeanGroup2}) / (n(1) + n(2)); \]

Finding the SCATTER Matrices for each class:

\[ \text{A} = n(1) * (\text{SampleMeanGroup1} - \text{OverallMean}) * (\text{SampleMeanGroup1} - \text{OverallMean})' \]
\[ \text{C} = n(2) * (\text{SampleMeanGroup2} - \text{OverallMean}) * (\text{SampleMeanGroup2} - \text{OverallMean})' \]
\[ \text{B} = (\text{A} + \text{C}); \]

Finding the Within-Groups Variability:

\[ \text{ScatterGroup1} = \text{scat(Group1Trainee)}; \]
\[ \text{ScatterGroup2} = \text{scat(Group2Trainee)}; \]
\[ \text{W} = \text{ScatterGroup1} + \text{ScatterGroup2}; \]
\[ \text{Mat} = \text{B} * \text{inv(W)} ; \]

Finding eigen values of matrix \( \text{inv(W)} \)*\text{B}:

\[ [\text{Eout DTemp}] = \text{eig(Mat)}; \]

Finding the highest eigen value and the corresponding Eigenvector:

\[ \text{T} = \text{diag(DTemp)}; \]
\[ [\text{maxeig indx}] = \text{max(T)} \]
\[ \text{EigVectFS} = \text{Eout(:,indx)}; \]
Spooled = W / ((SzTraineeG-1) + (SzTraineeN-1));
Check = EigVectFS' * Spooled * EigVectFS

% % % Transforming the Test set to this new single dimension
tempX = PCA_G(TestG,:);  
TestX = EigVectFS' * tempX;  
tempY = PCA_N(TestN,:);  
TestY = EigVectFS' * tempY;

----------------------------------------------------------------------------------------------------------------

ROC analysis of the given sample data based on the Fisher’s LDF output

Samples = [TestY,TestX];
nL = min(Samples) + 0.01;
nH = max(Samples) - 0.01;
Th = [nL:0.01:nH];
[Yaxis,Xaxis] = ROCanal(Samples,Th);
ROCArea = trapz(Xaxis,Yaxis)

%%% function for the ROC analysis of given test sample data
function [Yaxis,Xaxis] = ROCanal(Samples,Thresh)

NumSamples = length(Samples);
LengthG = length(Samples) / 2;
t =1;

for Th = Thresh
    clear Group1 Group2
    k1 =1;
    k2 =2;
    for i = 1 : NumSamples
        if(Samples(i) < Th)
            Group1(k1) = i;  
            k1 = k1+1;
        elseif(Samples(i) > Th)
            Group2(k2) = i;  
            k2 = k2+1;
        end
    end
end
Here True Pos = Has glaucoma (belongs to Group1) and has been identified in that group (assigned Group2)

\[ \text{TruePositive} = \frac{\text{sum}(\text{Group1} \leq \text{LengthG})}{\text{LengthG}}; \]

False Pos = Is Normal (belongs to Group2) and has been identified as having glaucoma (assigned Group1)

\[ \text{FalsePositive} = \frac{\text{length}(	ext{Group1}) - \text{sum}(	ext{Group1} \leq \text{LengthG})}{\text{LengthG}}; \]

True Neg = Is Normal (belongs to Group2) and has been assigned to Normal (Group2)

\[ \text{TrueNegative} = \frac{\text{sum}(\text{Group2} > \text{LengthG})}{\text{LengthG}}; \]

False Neg = Has Glaucoma (belongs to Group1) and has been assigned to Normal (Group2)

\[ \text{FalseNegative} = \frac{\text{length}(	ext{Group2}) - \text{sum}(	ext{Group2} > \text{LengthG})}{\text{LengthG}}; \]

Total number of samples

\[ \text{TotalSamples} = \text{length}(	ext{Group1}) + \text{length}(	ext{Group2}); \]

Specificity = TrueNegative;
Xaxis(t) = FalsePositive;
Sensitivity = TruePositive);
Yaxis(t) = Sensitivity;
PositivePredictiveValue = TruePositive/(TruePositive+FalsePositive);
t = t+1;
end

figure;
plot(Xaxis,Yaxis)
xlabel('1-Specificity')
ylabel('Sensitivity')
title('ROC Curve')