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Automatic Screening and Classification of Diabetic Retinopathy Eye Fundus Image

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Automatic Screening and Classification of Diabetic Retinopathy Eye Fundus Images

By

Sarni Suhaila Rahim

June 2016

Automatic Screening and Classification of Diabetic Retinopathy Eye Fundus Images

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Sarni Suhaila Rahim

June 2016

A thesis submitted in partial fulfilment of the University's requirements for the Degree of Doctor of Philosophy

ABSTRACT

Diabetic Retinopathy (DR) is a disorder of the retinal vasculature. It develops to some degree in nearly all patients with long-standing diabetes mellitus and can result in blindness. Screening of DR is essential for both early detection and early treatment. This thesis aims to investigate automatic methods for diabetic retinopathy detection and subsequently develop an effective system for the detection and screening of diabetic retinopathy.

The presented diabetic retinopathy research involves three development stages. Firstly, the thesis presents the development of a preliminary classification and screening system for diabetic retinopathy using eye fundus images. The research will then focus on the detection of the earliest signs of diabetic retinopathy, which are the microaneurysms. The detection of microaneurysms at an early stage is vital and is the first step in preventing diabetic retinopathy. Finally, the thesis will present decision support systems for the detection of diabetic retinopathy and maculopathy in eye fundus images. The detection of maculopathy, which are yellow lesions near the macula, is essential as it will eventually cause the loss of vision if the affected macula is not treated in time.

An accurate retinal screening, therefore, is required to assist the retinal screeners to classify the retinal images effectively. Highly efficient and accurate image processing techniques must thus be used in order to produce an effective screening of diabetic retinopathy. In addition to the proposed diabetic retinopathy detection systems, this thesis will present a new dataset, and will highlight the dataset collection, the expert diagnosis process and the advantages of the new dataset, compared to other public eye fundus images datasets available. The new dataset will be useful to researchers and practitioners working in the retinal imaging area and would widely encourage comparative studies in the field of diabetic retinopathy research. It is envisaged that the proposed decision support system for clinical screening would greatly contribute to and assist the management and the detection of diabetic retinopathy. It is also hoped that the developed automatic detection techniques will assist clinicians to diagnose diabetic retinopathy at an early stage.

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TABLE OF CONTENTS

ABSTRACT i
ACKNOWLEDGEMENTS ii
LIST OF FIGURES vi
LIST OF FIGURES FOR APPENDICES viii
LIST OF TABLES ix
LIST OF TABLES FOR APPENDICES x
LIST OF EQUATIONS x
LIST OF ABBREVIATIONS xi
LIST OF PUBLISHED PAPERS ON THIS RESEARCH xii
1 INTRODUCTION 1
1.1 Diabetic Retinopathy Screening and the Challenges Faced by the Malaysian Government 2
1.2 Research Aims and Objectives 5
1.3 Motivation and Contributions of the Thesis 8
1.4 Research Methodology 11
1.5 Thesis Overview 13
2 BACKGROUND AND LITERATURE REVIEW 15
2.1 Diabetes Mellitus 15
2.2 Diabetic Retinopathy 17
2.3 Epidemiology of Diabetic Retinopathy 21
2.3.1 Diabetic Retinopathy and Global Epidemiology 21
2.3.2 Diabetic Retinopathy Epidemiology in Malaysia 23
2.4 Classification of Diabetic Retinopathy 26
2.5 Diabetic Retinopathy Screening 27
2.5.1 Diabetic Retinopathy Grading 33
2.5.2 Examination Schedule 38
2.5.3 Diabetic Retinopathy Management and Treatment 40
2.6 Diabetic Retinopathy Image Processing 41
2.6.1 Image Preprocessing 41
2.6.2 Feature Extraction 47
2.6.3 Classification 51
2.6.3.1 Support Vector Machines 52
2.6.3.2 Neural Networks 53
2.6.3.3 Other Classification Methods 55
2.7 Fuzzy Image Processing 58
2.8 Summary 62
3 RESEARCH METHODOLOGY AND DATA COLLECTION 63
3.1 Research Design 63
3.2 Study Population 65
3.3 Location of the Research Study 65

3.4 Data Collection 65
3.4.1 Primary Data 66
3.4.2 Secondary Data 66
3.5 Collecting Data Procedure 67
3.5.1 Collecting Primary Data through Observation 67
3.5.2 Collecting Primary Data through Interview 69
3.5.3 Collecting Secondary Data through Existing Fundus Images 69
3.6 Data Management and Analysis Procedure 70
3.7 Ethical Considerations 71
3.8 Benchmark Public Data Sets 72
3.9 Developed Data Set 74
3.10 Summary 79
4 CONTRIBUTIONS TO DEVELOPING SYSTEMS FOR DIABETIC RETINOPATHY AND MACULOPATHY DETECTION 81
4.1 Basic System for General Diabetic Retinopathy Detection (System I) 82
4.1.1 Image Preprocessing 84
4.1.2 Feature Extraction 87
4.1.3 Classification 88
4.1.4 System Results and Evaluation 89
4.2 Microaneurysms Detection 91
4.2.1 Automatic Detection of Microaneurysms in Colour Fundus Images Using Vessel Segmentation and Features Extraction (System II) 91
4.2.1.1 Image Preprocessing 93
4.2.1.2 Feature Extraction 94
4.2.1.3 Classification 95
4.2.1.4 System Results and Evaluation 95
4.2.2 Automatic Detection of Microaneurysms in Colour Fundus Images Using a Combination of Image Preprocessing Techniques and Circular Hough Transform (System III) 97
4.2.2.1 Image Preprocessing 98
4.2.2.2 Circular Hough Transform 98
4.2.2.3 System Results and Evaluation 100
4.2.3 Automatic Detection of Microaneurysms in Colour Fundus Images Using Fuzzy Image Processing (System IV) 102
4.2.3.1 Image Preprocessing 103
4.2.3.2 Microaneurysms Detection 105
4.2.3.3 System Results 105
4.2.4 Automatic Detection of Microaneurysms Using Fuzzy Histogram Equalisation, Fuzzy Filtering and Fuzzy Edge Detection (System V) 107
4.2.4.1 Image Preprocessing 108
4.2.4.2 Localisation and Detection of Microaneurysms 111
4.2.4.3 Classification 111

4.2.4.4 System Results and Evaluation 112
4.3 Maculopathy and Diabetic Retinopathy Detection 114
4.3.1 Detection of Diabetic Retinopathy and Maculopathy in Eye Fundus Images Using Fuzzy Image Processing (System VI) 116
4.3.1.1 Image Preprocessing 118
4.3.1.2 Feature Extraction 119
4.3.1.3 Classification 120
4.3.1.4 System Results and Evaluation 120
4.3.2 Detection of Diabetic Retinopathy and Maculopathy in Eye Fundus Images Using Fuzzy Image Processing and Retinal Structures Segmentation (System VII) 122
4.3.2.1 Image Preprocessing 123
4.3.2.2 Retinal Structure Extraction 125
4.3.2.3 Exudate and Maculopathy Detection 129
4.3.2.4 Features Extraction 130
4.3.2.5 Classification 131
4.3.2.6 System Results and Evaluation 131
4.4 Summary 132
5 OVERALL RESULTS ANALYSIS AND DISCUSSION 135
5.1 Developed Data Set Analysis 135
5.2 System Results Analysis 140
5.2.1 Confusion Matrix 140
5.2.2 Statistical Analysis 141
5.3 Discussion 148
5.4 Summary 151
6 CONCLUSIONS AND FUTURE WORK 152
6.1 Review of the Work and Contributions 152
6.2 Future Work 155
6.3 Summary 158
REFERENCES 159
APPENDICES 171

LIST OF FIGURES

Figure 1.1 Methodology of the research 12

Figure 2.1 Retina (eyeSmart, 2014) 17

Figure 2.2 Diagrammatic representation of the different types of damage to capillaries in diabetic retinopathy (Taylor and Batey, 2012:24) (a) Normal capillary (b) Microaneurysm (c) Blot haemorrhage (d) Exudate 18

Figure 2.3 Features of diabetic retinopathy (Ministry of Health Diabetic Retinopathy Screening Team, 2012b) 20

Figure 2.4 Normal retina compared to retina with diabetic retinopathy signs 21

Figure 2.5 Global causes of visual impairment, including blindness, as percentage (World Health Organization, 2012b:6) 23

Figure 2.6 Global causes of blindness as a percentage of global blindness in 2010 (World Health Organization, 2012b:6) 23

Figure 2.7 Percentage distribution of diabetic retinopathy cases, glaucoma or lens-induced glaucoma, 2002-2013 (NED Steering Committee Members, 2015:112) .. 25

Figure 2.8 Diabetic retinopathy screening tools (Ministry of Health Diabetic Retinopathy Screening Team, 2012c:14) 29

Figure 2.9 Screening process of diabetic retinopathy to prevent blindness (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine of Malaysia, 2011) 31

Figure 2.10 Fundus camera photography (Ministry of Health Diabetic Retinopathy Screening Team, 2012b, 2012d) 32

Figure 2.11 Good quality fundus photos (Ministry of Health Diabetic Retinopathy Screening Team, 2012b) 32

Figure 2.12 Normal fundus image (Ministry of Health Diabetic Retinopathy Screening Team, 2012b) 33

Figure 2.13 Basic two-class classifications with Support Vector Machines (The Mathworks, Inc., 2016a) 53

Figure 2.14 Brightness Preserving Dynamic Fuzzy Histogram Equalization stages 59

Figure 2.15 Membership functions of the inputs and outputs (The Mathworks, Inc., 2016c) 61

Figure 2.16 Edge detection using fuzzy logic output (The Mathworks, Inc., 2016c) 61

Figure 3.1 Research development design 64

Figure 3.2 Research study location 66

Figure 3.3 Fundus images capturing and the grading process 68

Figure 3.4 Examples of images in the dataset 75

Figure 3.5 Expert diagnosis file 76

Figure 3.6 Expert diagnosis summary 76

Figure 3.7 Expert diagnosis average 77

Figure 3.8 Main web page for the developed dataset 78

Figure 4.1 Block diagram of the proposed general automatic screening and classification of diabetic retinopathy 83

Figure 4.2 Image preprocessing 87

Figure 4.3 Snapshot of the proposed system user interface 90

Figure 4.4 Block diagram of the proposed automatic detection of microaneurysms 92

Figure 4.5 Preprocessing the output image 94

Figure 4.6 Snapshot of the proposed system user interface 96

Figure 4.7 Block diagram of the proposed automatic detection of microaneurysms using Circular Hough Transform 98

Figure 4.8 Microaneurysms detection by using the Circular Hough Transform 99

Figure 4.9 Snapshot of the user interface of System III 100

Figure 4.10 Block diagram of System IV for the automatic detection of microaneurysms 104

Figure 4.11 Preprocessing the output image 104

Figure 4.12 Snapshot of the user interface of System IV 106

Figure 4.13 Block diagram of System V for the automatic detection of microaneurysms 108

Figure 4.14 Membership functions for inputs and outputs 110

Figure 4.15 Preprocessing the output image with fuzzy approaches 111

Figure 4.16 Snapshot of the proposed system user interface 113

Figure 4.17 Block diagram of System VI for the automatic detection of diabetic retinopathy and maculopathy using fuzzy image processing 117

Figure 4.18 Membership functions for inputs and outputs 118

Figure 4.19 Preprocessing of the output image 119

Figure 4.20 Snapshot of the proposed system user interface 121

Figure 4.21 Block diagram of System VII for the automatic detection of diabetic retinopathy and maculopathy using fuzzy image processing 123
Figure 4.22 Preprocessing the output image 125
Figure 4.23 Extraction of retinal structures 128
Figure 4.24 Exudates and maculopathy extraction output image 130
Figure 4.25 Snapshot of the proposed system user interface 132
Figure 5.1 Boxplot assessment 137
Figure 5.2 Histogram assessment 138
Figure 5.3 System development workflow 147

LIST OF FIGURES FOR APPENDICES

Figure A.1 Data collection and diabetic retinopathy screening process 171
Figure A.2 No diabetic retinopathy images 172
Figure A.3 Mild DR without maculopathy images 172
Figure A.4 Mild DR with maculopathy images 173
Figure A.5 Moderate DR without maculopathy images 173
Figure A.6 Moderate DR with maculopathy images 174
Figure A.7 Severe DR without maculopathy images 174
Figure A.8 Severe DR with maculopathy images 175
Figure A.9 Proliferative DR without maculopathy images 175
Figure A.10 Proliferative DR with maculopathy images 176
Figure A.11 Advanced diabetic eye disease images 176
Figure B.1 ‘Home’ page 184
Figure B.2 ‘About’ page 184
Figure B.3 ‘Team’ page 185
Figure B.4 ‘Publications’ page 185
Figure B.5 ‘Dataset’ page and ‘Download’ link 186
Figure B.6 ‘Contact’ page 186

LIST OF TABLES

Table 2.1 Terminology definition of diabetic retinopathy signs (adapted from Taylor and Batey, 2012) 19

Table 2.2 Sensitivity and specificity of diabetic retinopathy tools (Ministry of Health Malaysia, Malaysia Society of Ophthalmology and Academy of Medicine of Malaysia, 2011)..... 29

Table 2.3 Retinopathy stages and findings (Ministry of Health Diabetic Retinopathy Screening Team, 2012b) 34

Table 2.4 International Clinical Diabetic Retinopathy Disease Severity Scale (Wilkinson et al., 2003) 37

Table 2.5 Diabetic Macular Edema Disease Severity Scale (Wilkinson et al., 2003).... 38

Table 2.6 Timing of the first screening (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine of Malaysia, 2011) 39

Table 2.7 Recommended follow-up schedule (American Academy of Ophthalmology Retina Panel, 2008) 39

Table 2.8 Criteria for urgent referral (National Institute for Clinical Excellence, 2002)40

Table 2.9 Summary of treatment for diabetic retinopathy (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine of Malaysia, 2011) 40

Table 2.10 Summary of preprocessing techniques used in diabetic retinopathy screening research 43

Table 2.11 Summary of feature extraction methods used in previous diabetic retinopathy screening research..... 48

Table 2.12 Summary of machine learning techniques for classification used in previous diabetic retinopathy screening research 56

Table 3.1 Sensitivity, specificity and accuracy formula..... 71

Table 3.2 Expert diagnosis summary 77

Table 3.3 Summary of datasets used for systems development 80

Table 4.1 Feature extraction in the proposed system 88

Table 4.2 Average results when using the four classifiers 90

Table 4.3 Feature extraction in the proposed microaneurysms detection system 95

Table 4.4 Average results when using the four classifiers 96

Table 4.5 T-test analysis..... 101

Table 4.6 Chi-square analysis..... 101

Table 4.7 Summary results for Systems IV(a) and IV(b) 106
Table 4.8 Summary results for System V(a), V(b), V(c) and V(d) 113
Table 4.9 Summary results for System VI 121
Table 4.10 Average results when using the four classifiers 132
Table 5.1 Expert diagnosis summary categorisation 136
Table 5.2 ANOVA multiple comparisons 139
Table 5.3 Chi-square analysis 140
Table 5.4 Confusion matrix analysis of the proposed systems 142
Table 5.5 Inferential statistical analysis of the proposed systems 145

LIST OF TABLES FOR APPENDICES

Table A.1 Data collection methods 177
Table A.2 Data collection assessment 178
Table A.3 Expert diagnosis 179
Table A.4 Expert diagnosis summary 180
Table A.5 Findings summary 182
Table A.6 Discussion summary 183

LIST OF EQUATIONS

(4.1) 85
(4.2) 86

LIST OF ABBREVIATIONS

DM	Diabetes Mellitus
DR	Diabetic Retinopathy
DME	Diabetic Macula Edema
MOHM	Ministry of Health Malaysia
NPDR	Non-proliferative Diabetic Retinopathy
PDR	Proliferative Diabetic Retinopathy
WHO	World Health Organization
NHMS	National Health and Morbidity Survey
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
IRMAs	Intraretinal Microvascular Anomalies
NED	National Eye Database
SVM	Support Vector Machines
HOS	Higher Order Spectra
DWT	Discrete Wavelet Transform
ANN	Artificial Neural Network
D-FNN	Dynamic Fuzzy Neural Network
RBFNN	Radial Basis Function Neural Network
PNN	Probabilistic Neural Network
kNN	k-Nearest Neighbours
CNN	Convolutional Neural Networks

LIST OF PUBLISHED PAPERS ON THIS RESEARCH

Journal:

Rahim, S, S., Jayne, C., Palade, V., and Shuttleworth, J. (2015) 'Automatic Detection of Microaneurysms in Colour Fundus Images for Diabetic Retinopathy Screening'. *Journal of Neural Computing and Applications* 521, 1-16

Rahim, S. S., Palade, V., Shuttleworth, J., and Jayne, C. (2016) 'Automatic Screening and Classification of Diabetic Retinopathy and Maculopathy Using Fuzzy Image Processing'. in Zhong, N., and Peng, H. (ed.) *Brain Informatics* 40708, 1-19

Conference Papers:

Rahim, S. S., Palade, V., Shuttleworth, J., and Jayne, C. (2014) 'Automatic Screening and Classification of Diabetic Retinopathy Fundus Images'. in Mladenov, V. et al. (ed.) *Proceedings of 15th International Conference on Engineering Applications of Neural Networks, EANN 2014, Communications in Computer and Information Science* 459. held 5-7 September 2014 at Sofia, Bulgaria. Switzerland: Springer, 113-122

Rahim, S. S., Palade, V., Shuttleworth, J., Jayne, C., and Raja Omar, R. N. (2015) 'Automatic Detection of Microaneurysms for Diabetic Retinopathy Screening Using Fuzzy Image Processing'. in Iliadis, L., and Jayne, C. (ed.) *Proceedings of 16th International Conference on Engineering Applications of Neural Networks, EANN 2015, Communications in Computer and Information Science* 517. held 25-28 September 2015 at Rhodes, Greece. Switzerland: Springer, 69-79

Rahim, S. S., Palade, V., Jayne, C., Holzinger, A., and Shuttleworth, J. (2015) 'Detection of Diabetic Retinopathy and Maculopathy in Eye Fundus Images Using Fuzzy Image Processing'. in Guo, Y. et al. (ed.) *Proceedings of 8th International Conference on Brain Informatics and Health, BIH 2015, LNAI 9250*. held 30 August-2 September 2015 at London, UK. Switzerland: Springer, 379-388

1 INTRODUCTION

Diabetic Retinopathy (DR) is one of the diabetes complications and is an important cause of visual disability and blindness. It is vital to have a regular eye examination for initial detection and early treatment. This thesis is about the development of a medical decision support system for automatic diabetic retinopathy screening and classification in eye fundus images.

The scope of this research focuses on the Asian country of Malaysia. The research was sponsored by the Ministry of Higher Education in Malaysia and the Universiti Teknikal Malaysia Melaka (UTeM). In addition, the research also received support, particularly in the contribution of expertise, from the Department of Ophthalmology at the Melaka Hospital, Malaysia, under the Ministry of Health for Malaysia.

In order to develop an accurate and efficient diabetic retinopathy screening system, the capabilities of image processing techniques are investigated in this research work. Several highly efficient image processing techniques are implemented and tested to evaluate the system performance. The main image processing techniques used in this research involve fuzzy image processing on eye fundus images, which has not been previously investigated. A more reliable screening system can be produced with fuzzy image processing capability and therefore enable the achievement of the screening general aim, which is the earlier detection of sight threatening problems to ensure prompt treatment for the prevention of vision loss.

This chapter introduces diabetic retinopathy and its screening. It focuses on Malaysia and highlights some challenges faced by the Malaysian healthcare system in dealing with diabetic retinopathy screening. Section 1.2 presents the research aims and objectives. Section 1.3 explains the research motivation, alongside the contributions of the thesis. Finally, Section 1.4 presents the overview of the chapters of this thesis.

1.1 Diabetic Retinopathy Screening and the Challenges Faced by the Malaysian Government

Diabetic Retinopathy (DR) is a diabetes mellitus complication, which also include stroke, cardiovascular disease, diabetic nephropathy and diabetic neuropathy. The retinal capillaries damage occurs in diabetes mellitus. Diabetic retinopathy can be visualised only in the retina (Taylor and Batey, 2012), which is a layer of tissue. Diabetic retinopathy happens through lasting of small blood vessels damage in the retina, which eventually results in blindness. Hence, an effective screening of diabetic retinopathy is important for early treatment, as well as an effective management of risk factor to prevent diabetic complications.

The prevalence of diabetes globally presented by the World Health Organization (WHO), reported in 2014 was estimated to be 9% among adults aged 18 and above (2012a). Diabetes contributes to about one percent of global blindness (2012b). Globally, 4.8% of the 37 million blindness cases is caused by the diabetic retinopathy and approximately 366 million will be affected by diabetes mellitus worldwide in the year 2030 (World Health Organization, 2005). In addition, diabetes has also been predicted to be the seventh leading cause of death by the year 2030 (Mathers and Loncar, 2006). The initial National Health and Morbidity Survey I (NHMS I) for Malaysia was conducted in 1986. The survey reveals a prevalence of diabetes mellitus is 6.3%. In the year 1996, the percentage in NHMS II had increased to 8.3% and, the newest NHMS III 2006 report shows that the total diabetes mellitus prevalence is 14.9% (Letchuman et al., 2010).

Diabetes Mellitus (DM) is a complex disease resulting in severe complications in various parts of the body. Nevertheless, good control of DM will avoid or delay various complications, including diabetic retinopathy. The length of DM is associated with the diabetic retinopathy incidence, and it has been reported that more than 75% of diabetes patients have some diabetic retinopathy form after 20 years of the disease (World Health Organization, 2005). Thus, screening and early treatment can avoid significant loss of vision. Such efforts to control this enduring disease as well as the early complications detection such as diabetic retinopathy should be strengthened, because diabetic retinopathy is an asymptomatic condition in its initial stage (Taylor and Batey,

2012; Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine Malaysia, 2011). It is also stated that diabetics are twenty-five times more likely to develop blindness compared to the general population (Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia, 2002). Considering these complications and the rising numbers of diabetic patients in Malaysia, a programme of diabetic retinopathy screening in the country must be complete, covering all people with DM in Malaysia. To achieve this, significant resources will be required for the management of the condition including human resources, to increase the current workload within the field of disease diagnostics.

Diabetic retinopathy can only be identified through medical eye examination since it is asymptomatic in its initial stage. The diabetes management at the facilities of the Ministry of Health Malaysia (MOHM) is presently being performed in health clinics, in addition in polyclinics, specialised clinics as well as hospital wards. In Malaysia, screening is currently performed by general practitioners, clinicians in hospital based diabetes centres, ophthalmologists, optometrists or a technician and a medically trained photographic interpreter, in the case of photography (Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia, 2002). There are many modalities of screening available to detect and classify diabetic retinopathy. One of the most common techniques used is ophthalmoscopy. Non-mydriatic digital fundus photography is also popular (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine Malaysia, 2011).

Different screening modalities performed by different practitioners will produce a wide variation of sensitivity and specificity. The screening tools include the following: the direct and indirect ophthalmoscope, the slit lamp biomicroscope, the mydriatic fundus camera and the non-mydriatic fundus camera. The non-mydratic fundus camera has high sensitivity and specificity among other advantages. For example pupillary dilatation is not required, especially if the room is adequately darkened, promoting compliance, efficiency and safety (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine Malaysia, 2011). Trained primary care clinicians are needed for screening of diabetic retinopathy to increase the accuracy of

interpretation and grading. Proper training among all healthcare personnel therefore is essential. Specialised personnel for retinal screening and grading need specific training and regular performance assessment. Moreover, the Clinical Practice Guidelines Screening for Diabetic Retinopathy requires that the module of training should comprise clinical skills and knowledge, computer imaging and skills, in addition operational concerns and training of fundus grading (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine Malaysia, 2011).

Diabetes Mellitus is a growing problem among increasing numbers of diabetics every year. Subsequently, there are several challenges faced by the Ministry of Health Malaysia in diabetic retinopathy handling cases (Ministry of Health Malaysia, 2012a), including:

i. Inadequate diabetic eye screening programs

In order to perform successful eye screening, a team of trained healthcare personnel is required. Fewer screening teams, especially in rural hospitals, have significantly decreased the number of the eye screening programs. At the moment, screening programs are exclusively performed at primary health care centres (selected health clinic with fundus camera), hospital or clinics with eye care providers such as ophthalmology and optometry clinics. According to a relatively recent report on diabetic retinopathy screening by the Unit of Health Technology Assessment, only 24 out of the 114 Ministry of Health hospitals have a department of ophthalmology, while ophthalmologists aim to visits other hospitals regularly (Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia, 2002).

ii. Inadequate resources to complete the task

The main resources needed for the screening are trained staff and fundus cameras. All healthcare personnel involved in screening require proper training before they can join the programs. There is a need for training on

how to screen the images and how to improve the accuracy of interpretation and grading, in addition in terms of sensitivity and specificity.

The screening tools and techniques used in the program are the other important factors to be considered. There are many available screening modalities used for diabetic retinopathy screening. Ophthalmoscopy is a popular screening method, but non-mydriatic digital camera is also widely prescribed due to its high sensitivity and specificity. The fundus camera however is limited throughout Malaysian hospitals and health clinics. In the year of 2011, the total number of fundus camera available at health clinics under the Ministry of Health was only 107 (Ministry of Health Malaysia, Malaysian Society of Ophthalmology, Academy of Medicine Malaysia, 2011). This lack of vital screening resources will invariably result in longer waiting lists for initial screenings and referrals to ophthalmologist. This will ultimately lead to more serious eye complications.

iii. Poor patient information or awareness

One of the barriers in handling diabetic retinopathy is the patient factor. A lack of awareness of the possible eye complications from diabetes mellitus is one of the factors that have decreased the frequency of diabetic retinopathy screening. Moreover, other factors which impede the level of diabetic retinopathy awareness amongst Malaysians are eye care services poor access and dissimilar cultural beliefs. As such, patients should be aware that regular eye examinations are important.

1.2 Research Aims and Objectives

The aim of this research is to investigate automatic methods for diabetic retinopathy detection that can contribute towards improving diabetic retinopathy management and, subsequently, to develop an efficient system for diabetic retinopathy screening. Basically, the proposed diabetic retinopathy research consists of three types of systems. Firstly, the thesis will present the development of a basic system for the screening and classification of diabetic retinopathy using eye fundus images, which is a system for

general detection for diabetic retinopathy screening and will classify images into two respective cases: Normal and Diabetic Retinopathy. The research will then focus on the microaneurysms detection which are the earliest diabetic retinopathy signs.

Different image processing techniques, including fuzzy image processing, are implemented in a variety of detection systems for microaneurysms which classify images into two main categories. The first categorisation classifies them into detected and non-detected cases. The second categorisation is based on Normal (No DR) and Diabetic Retinopathy cases. In addition, the thesis presents the fuzzy-based image processing decision support systems for diabetic retinopathy and maculopathy detection in eye fundus images. The proposed systems classify the images into two types of classification, in order to generate a diversity of results and system performance analysis, which are the two above cases (Normal and Diabetic Retinopathy) and an additional ten cases which follow the ophthalmologists' practice and provide more details. The second classification involves No Diabetic Retinopathy and the other nine detailed classes of the DR cases: Mild DR without maculopathy, Mild DR with maculopathy, Moderate DR without maculopathy, Moderate DR with maculopathy, Severe DR without maculopathy, Severe DR with maculopathy, Proliferative DR without maculopathy, Proliferative DR with maculopathy and Advanced Diabetic Eye Disease (ADED).

In order to assist screeners to classify the retinal images effectively and with high confidence, an accurate retinal screening system is necessary. Therefore, to develop a diabetic retinopathy screening grading and classification system, effective techniques of image processing must be used. This research project examines the use of the fundus images for detecting the diabetic retinopathy features presence in the eyes. This is a particularly challenging problem and this thesis proposes novel use of image processing techniques in order to automatically detect the stages of retinopathy. To achieve this aim, highly efficient and accurate image processing techniques must be used to produce an effective screening of diabetic retinopathy.

Despite the existence of a range of image processing techniques, the need for highly effective and specialised image processing techniques in this case cannot be over emphasised. Factors such as the fundus images suffering from noise and latency are often encountered, necessitating calibration and filtering before the images can be used reliably. In addition, the quality of the image depends on the skills applied by the paramedic in capturing the eye fundus images, as well as on other factors including the quality of the equipment and possible distractions from the environment. Due to these facts, all healthcare staff requires proper training before they are qualified and equipped for diabetic retinopathy screening. This is important as it can help increase the likelihood of accurate interpretation and grading. In addition to the lengthy and rigorous training of healthcare personnel before qualification, a growing challenge faced by the healthcare sector is the fact that diabetes mellitus is on the increase, with higher numbers of diabetics each year. It has also been highlighted by governments and other relevant stakeholders that the diabetic eye screening program is inadequate, as are the resources to complete the task, in addition to poor patient information or awareness (Ministry of Health Diabetic Retinopathy Screening Team, 2012b).

Further to the range of complications associated with images captured by the fundus camera, there is also the need for an experienced paramedic to diagnose whether the patient has any conditions (i.e., diabetic retinopathy). This screening phase is carried out manually by the paramedic who looks for any changes (abnormalities) on the retinal image, making the whole diagnostic process highly convoluted and protracted.

Based on the aforementioned reasons, in order to pursue this study primary research outcome, which is the development of a computer-based imaging tool, a method must be created in order to effectively detect important features on the fundus images and efficiently classify patients into the correct retinopathy stages. This automatic diabetic retinopathy grading will facilitate a reduction in the burden of manual grading for the screening team, and help alleviate the pressure on the limited eye screening centres in Malaysia (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine Malaysia, 2011). As a result of early detection, it would also help ophthalmologists to treat patients before their conditions worsen and, most importantly,

increase the chance of protecting the patient's vision. Moreover, an automatic diabetic retinopathy system would diagnose it in a faster and more efficient way. In addition, as suggested by the available literature, the initial detection of retinopathy, the existing retinopathy monitoring with consistent fundus examinations and effective laser treatment at suitable times, are among the key measures to prevent visual loss from diabetic retinopathy (Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia, 2002).

The main objectives of the research described in this thesis are as follows:

i. To develop an automatic screening and classification systems for diabetic retinopathy using fundus images in order to detect diabetic retinopathy at an early stage.
ii. To propose novel use of image processing and machine learning techniques for early detection of the signs of diabetic retinopathy.

The research introduced novel use of image processing techniques for the automated detection of retinopathy stages, including the combination of various pre-processing techniques as well as fuzzy image processing techniques, such as fuzzy histogram equalisation, fuzzy filtering and fuzzy edge detection. In addition, the research proposed the use of Circular Hough Transform and various machine learning classifiers.

1.3 Motivation and Contributions of the Thesis

Eye screening is important for the early detection and treatment of diabetic retinopathy. Regular screening can help detect patients with diabetes at an early stage thus, earlier identification of any retinopathy can allow changes in blood pressure or blood glucose to be managed efficiently to slow the rate of progression of the disease. The importance of the proposed research is to overcome the current problems faced in the diabetic retinopathy screening process, such as:

i. Manual diagnosis by the ophthalmologist

Currently, clinicians use non-mydratic fundus cameras to capture retinal images. Based on the image produced from the fundus camera, the experienced screening team will diagnose whether or not patients have any conditions (including diabetic retinopathy). The diagnosis is carried out manually by screeners who assess any changes (abnormalities) on the retinal image. This process is both laborious and prone to error. Therefore, a computer-based imaging tool is needed to effectively detect the signs of diabetic retinopathy, allowing ophthalmologists to gain a suitable window in which to treat patients, before serious damage occurs, thus increasing the chance of protecting the patient's vision. It will also help decrease the workload for healthcare personnel in the diabetic retinopathy screening process.

ii. Time taken and limitations of screening resources

The proposed automatic diabetic retinopathy system would help save time, costs and ultimately the vision of patients. With appropriate automation (i.e., decision support systems) in place, preventative actions to protect vision can then be taken earlier and therefore can help reduce the number of diabetic retinopathy problems, in addition to the risk of blindness. A decision support system for clinical diagnosis would contribute greatly in assisting with the management and detection of diabetic retinopathy. An automatic system will assist an ophthalmologist (or optometrist) to detect diabetic retinopathy (and its detailed classification) in a more efficient and faster way compared with manual analysis, which is more time-consuming. As a result, the proposed system will indirectly assist in the process of recommended follow-up schedules for each category of diabetic retinopathy based on the system detection. Furthermore, the development of the proposed system will contribute to overcoming the diabetic retinopathy screening limitations inherent in the present manual screening procedure, especially given the problems of inadequately trained staff and the use of the fundus camera, as highlighted in Section 1.1.

iii. Developing effective techniques of image processing for the diabetic retinopathy detection

Diabetic retinopathy screening is a popular research area and many researchers focus on and contribute to the advancement of this study area. Most researchers focus on finding and proposing an accurate technique or method for detecting certain features of diabetic retinopathy through exploring the eye fundus images. Although there have been immense advancements in this area of research, there are still lacunae or spaces for improvement. The proposed techniques in this research will most notably benefit the realm of image processing in a number of areas or ways that include the provision of an accurate method for effectively detecting features of diabetic retinopathy.

Based on the general objectives in Section 1.2 above, in particular the second objective, the highlighted contributions of this thesis include: implementing image processing techniques combination for the general diabetic retinopathy screening detection (Rahim et al., 2014), investigating image processing techniques combination for the diabetic retinopathy features detection, focusing on microaneurysms, an important early feature of diabetic retinopathy (Rahim et al., 2015a; 2015b) and the evaluation of image processing techniques combination for the diabetic retinopathy and diabetic maculopathy detection (Rahim et al., 2015c; 2016). In addition, the contributions of this thesis include employing the novel use of fuzzy image processing techniques for the pre-processing stage of medical images, i.e., eye fundus images for diabetic retinopathy screening (Rahim et al., 2015a; 2015b; 2015c; 2016), as well as implementing a new online dataset containing normal and diabetic retinopathy fundus images (Rahim et al., 2015b; 2015c; 2016) and finally, testing a new method for macula region localisation in order to detect maculopathy (Rahim et al., 2016).

To summarise, diabetes mellitus is a main health problem. One of the diabetes mellitus health effects is diabetic retinopathy, which causes blindness. Therefore, an effective

tool to help in the diabetic retinopathy detection is essential. A computer-based imaging screening method is needed to be developed where effective and cost-effective approaches are required. Automatic detection systems of diabetic retinopathy for patients with diabetes using the eye fundus photography will help the screening process by providing a user- or patient-friendly approach in addition to a cost-effective screening tool. Automatic classification systems with a high accuracy of diabetic retinopathy screening will help in decreasing the workload for healthcare personnel in the process of the early detection of diabetic retinopathy. It would also be helpful to patients in terms of early treatment, which could prevent or ameliorate substantial visual loss. This thesis proposes an automatic diabetic retinopathy detection system, and also introduces a new dataset of fundus images, which would be beneficial to retinal imaging researchers and practitioners, especially in the diabetic retinopathy screening field.

1.4 Research Methodology

The research methodology is concerned with the base of the inverted triangle in Figure 1.1. The figure shows that the main components of this research are diabetic retinopathy screening, fundus images as input and image processing techniques. The developed system consists of three stages: image pre-processing, feature extraction and classification. In order to validate the systems output performance, the results generated from the developed system are compared to the expert findings and several analyses are performed.

Understanding the diabetic retinopathy screening process, including the diabetic retinopathy development and diabetic retinopathy signs, are essential and information is collected through observation and interview techniques. The fundus images, which are the main data for this research, are extracted from the personal computer that is attached to the fundus camera. Each patient folder consists of the patient information and the eye fundus images. The automatic diabetic retinopathy detection systems are developed by employing a novel use of image processing techniques. The developed systems consists of three types of system development, which are the general detection of diabetic retinopathy, the development of an automatic system for microaneurysms detection and the development of an automatic diabetic retinopathy and maculopathy detection

system. The systems are evaluated with the combination of normal and diabetic retinopathy fundus images from a new data set collected during this research and also from several public datasets available as benchmark data. A thorough system performance analysis has been undertaken, which compared the performance of automatic systems to the manual diagnosis performed by the experts.

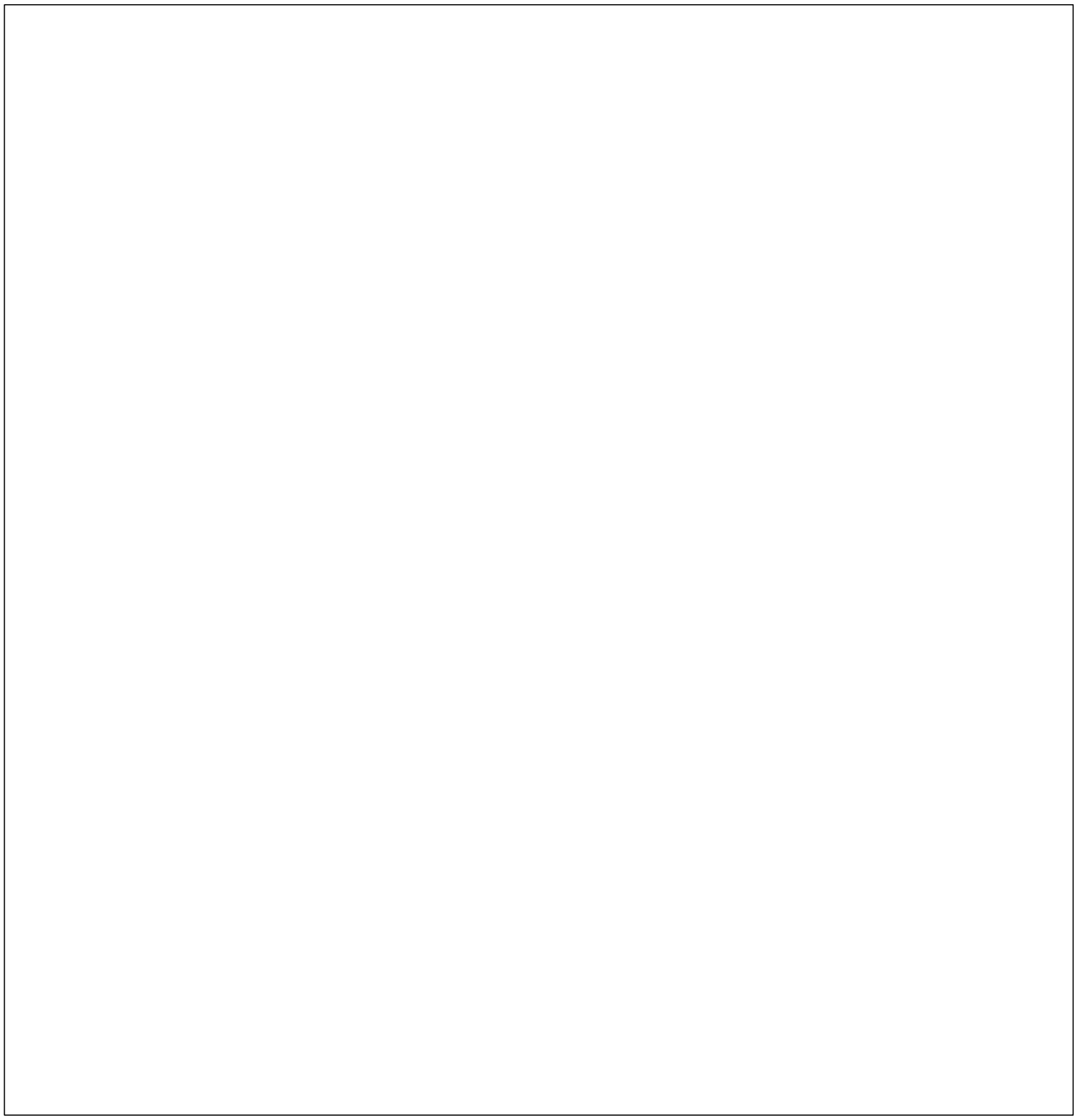

Figure 1.1 Methodology of the research

1.5 Thesis Overview

The thesis is organised into six chapters, each focusing on different features of the research work. The following is a summary of the contents of each chapter.

Chapter 1 provides an overview of diabetic retinopathy screening and a more detailed investigation of the problems, particularly in Malaysia. The research aims and objectives of this study are also presented. In addition, the motivations which have led to this research, the contributions of the thesis and the research methodology are presented in this introductory chapter.

Chapter 2 describes the background and the literature review in addition to basic information on diabetes mellitus and diabetic retinopathy, as well as the prevalence of diabetes mellitus and diabetic retinopathy worldwide and, particularly, in Malaysia. It also provides information on the level of advancement in the area of image processing for diabetic retinopathy screening systems. The chapter also highlights the implementation of fuzzy image processing techniques on medical and non-medical images, which is the core of this research work.

Chapter 3 discusses the research methodology used, including the process of data collection for this study. The research design, as a guide for planning the research development, is also presented. The experimental datasets, which consist of the existing datasets and a novel developed dataset, are presented in Chapter 3 in greater detail. The development of this new dataset is highlighted, including the expert diagnosis process, the diagnosis summary and its overall advantages.

Chapter 4 explains the development of the proposed systems, using the previously described datasets and image processing techniques. Each system presents a combination of different techniques, such as different pre-processing techniques, different feature parameters and different classifiers in the diabetic retinopathy screening system. These systems are different from those proposed by other researchers. The evaluations of the developed systems are also presented in Chapter 4, where it

presents the efficiency and the validity of diabetic retinopathy classification through the developed systems.

Chapter 5 presents the overall results analysis of a new dataset. It also presents the overall result analysis for the automatic developed systems. The chapter discusses the analysis performed on the expert diagnosis, including descriptive and inferential analysis. In order to generate a variance of system testing results and system performance, the overall analysis of the developed systems are presented in two ways: confusion matrix and statistical analysis. In addition, some discussions on the findings of this study are presented.

Chapter 6 summarises the accomplishments of the research work. It concludes the contents of the thesis and also highlights some recommendations for future research work. It also provides information regarding the research contributions, which have benefited a number of areas.

2 BACKGROUND AND LITERATURE REVIEW

Diabetes Mellitus (DM) is a significant public health concern. The diabetes epidemic is leading to an increasing number of severe and chronic complications, including those that are sight-threatening. Diabetic Retinopathy (DR) is a complication of diabetes caused by high blood glucose. Diabetic retinopathy is a microvascular complication of both insulin dependent (type 1) and non-insulin dependent (type 2) diabetes. It is one of the diabetes mellitus complications that damages blood vessels inside the retina. The retina is located at the back of the eye. Diabetic retinopathy commonly affects both eyes and can lead to vision loss if it is not promptly treated (Centre for Eye Research Australia, 2013).

This chapter provides the background for each of the main components involved in the research. It comprises seven main components which are diabetes mellitus, diabetic retinopathy, epidemiology of diabetic retinopathy, classification of diabetic retinopathy, diabetic retinopathy screening, diabetic retinopathy image processing and finally, fuzzy image processing, particularly on medical images. The chapter starts with the explanation of diabetes mellitus in Section 2.1, followed by Section 2.2 which presents one of its complications, i.e., diabetic retinopathy. Section 2.3 reveals the prevalence of diabetes mellitus and diabetic retinopathy from a global perspective in addition to an epidemiologic perspective in Malaysia. The classification of diabetic retinopathy is explained in Section 2.4. Section 2.5 describes how diabetic retinopathy screening is performed, including the grading process, examination schedule, diabetic retinopathy treatment and management in addition to the follow up schedule. The image processing approach, which is particularly used in diabetic retinopathy screening research, is explained in Section 2.6. The implementation of fuzzy image processing that focuses on medical images, which is the core of the proposed research, is presented in Section 2.7. Finally, a summary of the second chapter is provided in Section 2.8.

2.1 Diabetes Mellitus

Diabetes mellitus is a disorder caused by constant hyperglycemia of variable severity, incidental to a lack or lessened efficacy of insulin (Ministry of Health Diabetic

Retinopathy Screening Team, 2012a). Meanwhile, Scanlon et al. (2012) have defined diabetes mellitus as a chronic condition due to an excess of glucose circulating in the bloodstream. Diabetes is a disorder caused by high levels of glucose in the blood (Taylor and Batey, 2012; NHS Choices, 2012). It happens either when the pancreas does not produce enough insulin or because cells do not respond to the insulin produced. Insulin is a peptide hormone, produced by beta cells of the pancreas, a large gland which is located behind the stomach. There are two types of diabetes mellitus, which are Type 1 diabetes and Type 2 diabetes.

The increasing numbers of cases of diabetes are due to the following factors: a longer life-span, modern lifestyles (urbanisation, mechanisation and industrialisation) and also environmental and social factors, such as an unhealthy diet, obesity and physical inactivity (International Diabetes Federation, World Health Organization and Secretariat of the Pacific Community, 2000; Ministry of Health Diabetic Retinopathy Screening Team, 2012a; Sivaprasad et al., 2012), in addition to uncontrolled hypertension and smoking (Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia, 2002). Tajunisah and others (2006) have claimed that the duration of diabetes, hypertension and systemic complications including diabetic foot ulcer, lower limb amputation, nephropathy and neuropathy were also factors of retinopathy incidence. In addition, Mallika et al. (2011) confirmed that the duration of diabetes, body mass index and visual loss are associated with diabetic retinopathy. Meanwhile, the main symptoms of both types of diabetes are thirst, urinating frequently (particularly at night), tiredness, weight loss, loss of muscle bulk, skin infections and urinary infections (NHS Choices, 2012; Taylor and Batey, 2012).

Diabetes causes capillaries problems in the body, and the merely way to visualise this condition is by looking into the retina (Taylor and Batey, 2012). Figure 2.1 shows the anatomy of the eye including the retina, optic nerve, retinal vessels, cornea, lens, iris and sclera. The retina is a light-sensitive tissue that located at the back of the eye, as illustrated in Figure 2.1. Diabetes mellitus, if left untreated, can cause many health problems. Among the systemic complications of diabetes mellitus are stroke,

cardiovascular disease, diabetic neuropathy, diabetic nephropathy and also diabetic retinopathy (Ministry of Health Diabetic Retinopathy Screening Team, 2012a).

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Figure 2.1 Retina (eyeSmart, 2014)

2.2 Diabetic Retinopathy

The clinical manifestations of retinopathy are due to two basic pathophysiologic mechanisms: increased capillary penetrability and the closure of the retinal capillaries (Health Technology Assessment Unit, Medical Development Division Ministry of Health Malaysia, 2002). Meanwhile, Taylor and Batey (2012) defined the term 'retinopathy' as a disease of the retina, and explained how diabetic retinopathy occurs. High levels of blood sugar eventually cause capillary damage, where the lining cells of capillaries become activated and 'leaky'. Capillary closure or occlusion happens later, due to the capillary damage and also the increase of the platelet stickiness and clotting factors. As a result, the capillaries fail to supply nutrients to the retina as usual and produce ischaemia, which is a decreased blood flow.

Figure 2.2 illustrates certain problems in diabetic retinopathy that are caused by the capillary damage. Part (a) of Figure 2.2 shows a normal capillary, while part (b) shows a microaneurysm, formed by the ballooning of a weak part of the capillary wall, which appears as a dot to the observer. Part (c) visualises a blot haemorrhage due to the leakage of blood from a damaged capillary and appears as a rounded blot to the observer. An exudate is shown in part (d), where resulting from a leaky capillary wall, more plasma than usual escapes from the capillary. The exudates appear as a white lesion, as the pressure causes blood to squeeze from all the surrounding capillaries.

Diabetic retinopathy lesions, as illustrated in Figure 2.2, definition of some other diabetic retinopathy lesions in addition to several terms related to the diabetic retinopathy process are explained in Table 2.1.

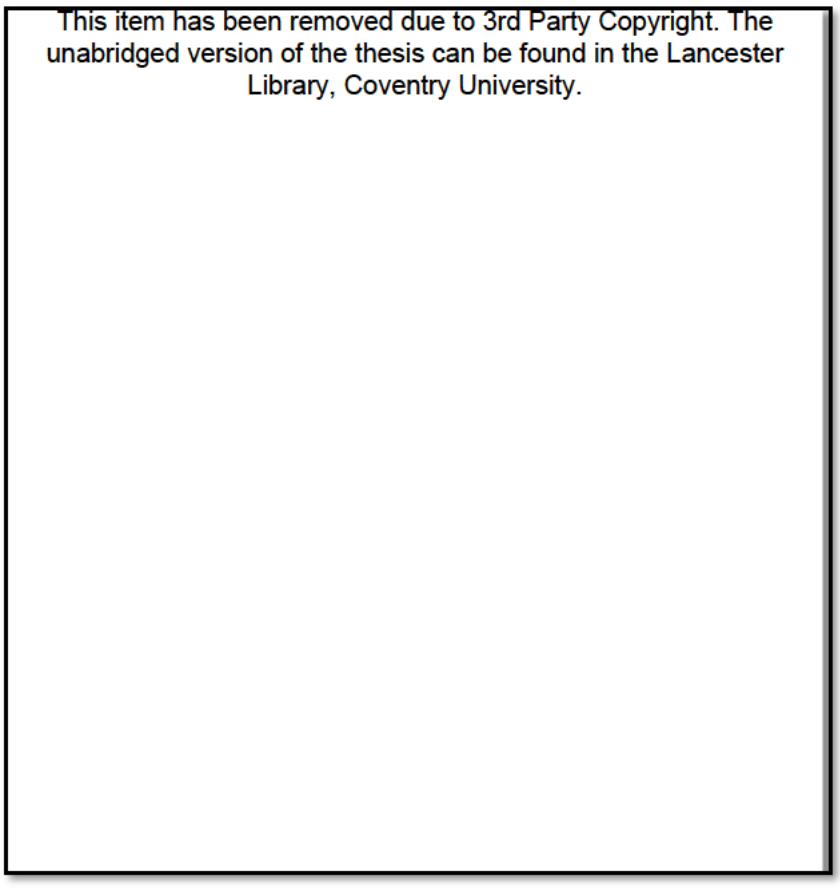

Figure 2.2 Diagrammatic representation of the different types of damage to capillaries in diabetic retinopathy (Taylor and Batey, 2012:24) (a) Normal capillary (b) Microaneurysm (c) Blot haemorrhage (d) Exudate

A fundus image with diabetic retinopathy features is presented in Figure 2.3, while the explanation of the features is presented in Table 2.1. Amongst the detected retinopathy signs are the microaneurysms, the retinal haemorrhages, the hard exudates, cotton wool spots, abnormal new vessels and venous beadings, which are presented in Figure 2.3. The definitions of these signs of diabetic retinopathy are listed in Table 2.1.

Table 2.1 Terminology definition of diabetic retinopathy signs (adapted from Taylor and Batey, 2012)

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Table 2.1 (continued)

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Figure 2.3 Features of diabetic retinopathy (Ministry of Health Diabetic Retinopathy Screening Team, 2012b)

Figure 2.4 shows a comparison between the ordinary retina and a retina with diabetic retinopathy signs. Figure 2.4 (a) shows the normal retina, which is free of any signs of diabetic retinopathy. Meanwhile, Figure 2.4 (b) shows the retina with the presence of several features of diabetic retinopathy, such as microaneurysms, haemorrhages, exudates, cotton wool spots and maculopathy. The terminology of these features is described in Table 2.1, while the visualisation of these features is presented in Figure 2.3.

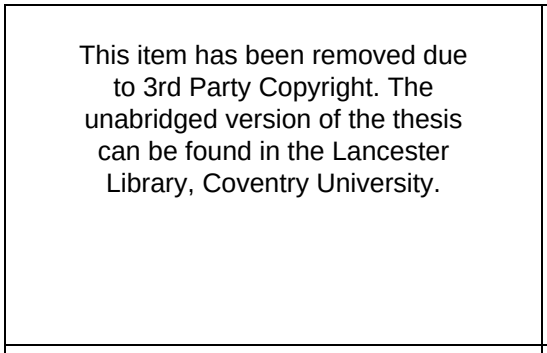	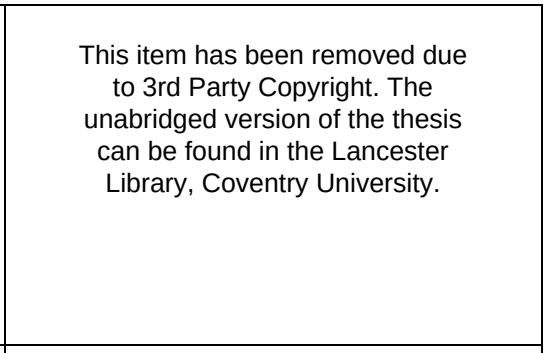
(a) Normal retina	(b) Diabetic retinopathy signs

Figure 2.4 Normal retina compared to retina with diabetic retinopathy signs

2.3 Epidemiology of Diabetic Retinopathy

This section will reveal both the Malaysian and the worldwide prevalence of visual impairment and diabetic retinopathy.

2.3.1 Diabetic Retinopathy and Global Epidemiology

Diabetic Retinopathy is an important cause which can lead to blindness. Global Data on Visual Impairment, a 2010 article by the World Health Organization (WHO) stated that globally, the number of visually impaired people of all ages was estimated to be 285 million, where 39 million are blind and 246 million suffered from low vision (World Health Organization, 2012b). In addition, people aged 50 years and older make up 82%

of the blind and 65% of the visually impaired. The report makes estimates for three age groups (0 to 14 years, 15 to 49 years and 50 years above) coming from six WHO regions (the African Region, the Region of the Americas, the Eastern Mediterranean Region, the European Region, the South-East Asian Region and the Western Pacific Region). The major global causes of visual impairment are uncorrected refractive errors (42%), cataracts (33%), glaucoma (2%), age related macular degeneration (1%), diabetic retinopathy (1%), trachoma (1%), corneal opacities (1%) and the remaining 18% is undetermined. Meanwhile, the major causes of blindness are cataracts (51%), glaucoma (8%), age related macular degeneration (5%), childhood blindness (4%), corneal opacities (4%), uncorrected refractive errors and trachoma (3%), diabetic retinopathy (1%) and other undetermined causes (21%). The global visual impairment and blindness reasons are depicted in pie chart form in Figure 2.5 and Figure 2.6, respectively. The report summarises that retinal diseases are the main global of visual impairment cause. In addition, the article confirms that the total number of visual impairments and blindness due to age-related macular degeneration, glaucoma and diabetic retinopathy is more compared to trachoma and corneal opacities, which are the infective causes. The report suggests an urgent development of the eye care system including rehabilitation, education and support services is required to overcome those enduring eye diseases. It can be concluded therefore that diabetic retinopathy is among of the visual impairment and blindness causes. Thus, this eye problem should be addressed before it is worsens.

In addition, Sivaprasad and others (2012) examine a global prevalence of diabetic retinopathy according to ethnicity and region. The survey reveals that the prevalence of diabetic retinopathy, including sight threatening diabetic retinopathy and macular edema, are higher in South Asian, African and Latin American populations compared to the white population. The survey also concludes that ethnic-specificity is one of the contribution rates of diabetic retinopathy, in addition to other factors, including the length of exposure and severity of hyperglycemia, hypertension and hyperlipidemia. In addition, factors like obesity, urbanisation, changes in diet, sedentary lifestyles and communicable diseases rate will increase the demands on healthcare for many ethnicities, particularly in Asia.

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Figure 2.5 Global causes of visual impairment, including blindness, as percentage (World Health Organization, 2012b:6)

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Figure 2.6 Global causes of blindness as a percentage of global blindness in 2010 (World Health Organization, 2012b:6)

2.3.2 Diabetic Retinopathy Epidemiology in Malaysia

Diabetes mellitus is a significant public health concern and one of the most established enduring diseases in Malaysia. The National Health and Morbidity Survey (NHMS) presented the diabetes prevalence for Malaysians (Letchuman et al., 2010). The survey,

which involved 34,539 respondents and covered all states of Malaysia, reported that the highest prevalence of diabetes among ethnic groups is thus: Indians (19.9%), followed by Malays (11.9%) and Chinese (11.4%). In addition, the survey also revealed other information, such as the prevalence of people with known diabetes was 7.0%, while newly diagnosed diabetes was 4.5% and 4.2% for Impaired Fasting Glycaemia. It was also reported that about 73.5% of the patients used the government healthcare services and only 45.05% of known diabetics had undergone an eye examination. Letchuman and others (2010) were unsatisfied with the results showing that only one third of respondents had their eyes examined within one year from the time of the survey. Although they are required to have an eye examination at diagnosis and subsequently annually (as recommended by the clinical practice guidelines on the management of diabetic retinopathy in type 2 diabetes), the patients seldom had their eye examinations as suggested. In addition, Letchuman and others (2010) conclude that the reasons for the lower percentage of eye examination are include: patients' lack of awareness of the schedule and the lack of eye screening services due to insufficient numbers of trained staff and resources.

The survey also reported the prevalence of diabetes cases in Malaysia by state, where Negeri Sembilan, Melaka and Penang have the highest frequency of diabetes, with 15.3%, 15.2% and 14.9%, respectively. The location of this research is Melaka, which is highlighted as having the highest prevalence of diabetes. The survey also reveals that the prevalence of diabetes is higher in urban (12.2%) compared to rural areas (10.6%). In addition, Mafauzy and colleagues (2011) proposed a study on the diabetes care status in Malaysia, which involved 1,670 patients from general hospitals, diabetes clinics and referral clinics. The most commonly reported eye complications of the study include proliferative diabetic retinopathy.

Goh's research (2008) reported that in 2007 the total number of diabetics with diabetic retinopathy registered to the Diabetic Eye Registry was about 36.8%. In addition, the research revealed some demographic characteristics, such as the mean age of the registered patients was 57.2 years and that half of them (52.8%) were aged between 30 to 60 years. Diabetic patients were most commonly female at 54.6% and the majority of

the patients were Malay (54.0%). Moreover, about 92.2% of patients diagnosed with type 2 diabetes mellitus had the condition for below 10 years and 91.7% had been referred from a government healthcare facility. It was also reported that two thirds of diabetic patients had never previously undergone an eye examination and 71.9% of those who had an eye examination had attended a year ago. There were about 63.3% patients diagnosed as having no diabetic retinopathy, in addition to mild non-proliferative diabetic retinopathy accounting for 16.5%, moderate non-proliferative diabetic retinopathy (9.8%), severe non-proliferative diabetic retinopathy (3.4%), proliferative diabetic retinopathy (7.1%) and maculopathy was detected in 9.5% of cases (Goh, 2008).

The 7th Report of the National Eye Database 2013 by the NED Steering Committee Members (2015) presented the distribution of three eye diseases, which consisted of diabetic retinopathy, glaucoma and lens-related complications, from the year 2002 to 2013, as illustrated in Figure 2.7. It can be concluded that among the three eye diseases, diabetic retinopathy showed the highest percentage of distribution. The percentage of diabetic retinopathy cases however, seemed to be reducing from 2010 onwards.

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Figure 2.7 Percentage distribution of diabetic retinopathy cases, glaucoma or lens-induced glaucoma, 2002-2013 (NED Steering Committee Members, 2015:112)

In addition, Addoor and others (2011) conducted a study of the awareness of diabetic retinopathy among the patients attending the diabetic clinics in Melaka, Malaysia and reported that 79.8% of the respondents were aware of diabetes mellitus complications and 87.2% were aware that diabetes can affect the eyes. The study also reported however that only 50% of the patients had undergone an ophthalmological evaluation. The proposed study concluded that although awareness among the patients was good, the motivation to undergo the assessment was poor. Furthermore, Thevi et al. (2012) revealed the eye diseases and visual impairment frequency among the rural population. It was reported that cataracts (22.9%) were the most popular eye disease, after that retinal illnesses including diabetic retinopathy (11.5%) and ocular trauma (9.8%).

2.4 Classification of Diabetic Retinopathy

There are several classifications or stages of diabetic retinopathy. The Screening for Diabetic Retinopathy Report by the Ministry of Health in Malaysia explained the technical features of how the stages of diabetic retinopathy occur (Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia, 2002). The enlargement of the veins in the retina is reported as one of the initial signs of diabetic retinopathy. The small capillaries present may also produce some changes, which affect the blocking, and later result in small swellings in the vascular walls, called microaneurysms. This is termed minimal non-proliferative diabetic retinopathy (NPDR), and, at this early stage, the sight may not be affected. The incidence of diabetic retinopathy continued in cases where the blood flow gradually worsens and progressively causes damage to larger portions of the retina. At this level, small haemorrhages and other vascular changes in the fundus of the eye appear, due to vascular blocking and leakage. Consequently, the retinopathy progresses from minimal to mild, due to the appearance of retinal haemorrhages, hard exudates and nerve layer infarct. In addition to minimal and mild NPDR, moderate NPDR occurs due to venous beading and intra-retinal microvascular irregularities. For severe NPDR classification, there should be more haemorrhages, microaneurysms, intra-retinal microvascular abnormalities and venous beading than is present in moderate NPDR (Health Technology Assessment Unit, Medical Development Division, Ministry of Health Malaysia, 2002).

The next severe stage of diabetic retinopathy, or proliferate diabetic retinopathy (PDR) occurs when new vessels (neovascularisation) are detected. This stage is high risk and could result in blindness. These diabetic retinopathy stages and their respective features are presented in Table 2.4. The macula disorders which affect the central vision happen due to visual loss from diabetic retinopathy. Therefore, eye examinations for the diagnosis of diabetic retinopathy at an initial stage are important, because diabetic retinopathy can bring to blindness. Moreover, regular screening can help save sight.

2.5 Diabetic Retinopathy Screening

Screening is defined as the testing of a population in order to identify individuals exhibiting attributes that could be early symptoms, or indicators, of a predisposition associated with a particular condition (Taylor and Batey, 2012). The main purpose of diabetic retinopathy screening is to detect whether the individuals require referral for further treatment, in order to prevent blindness (Taylor and Batey, 2012). In addition to this main purpose, there are other purposes for diabetic retinopathy screening. These include: identifying the disease at an early stage; possibly detecting a requirement for blood pressure and blood sugar treatment; educating the population about the causes of diabetic retinopathy and ways to reduce the risk; and, potentially, to identify non-diabetic conditions through the screening process (Taylor and Batey, 2012). One major problem is that diabetic eye disease does not interfere with sight until it reaches an advanced stage (Taylor and Batey, 2012). Laser treatment can save sight, but only if it is used at an early stage. This shows the importance of essential regular screening, which can help detect the diabetic patients at an early stage of diabetic retinopathy. Moreover, earlier identification of any retinopathy signs can allow changes to blood pressure or blood glucose management in order to slow the rate of progression.

Digital retinal imaging is usually used as a screening technique. The proposed method is recommended in the UK and also by the National Retinal Screening Project Group (Taylor and Batey, 2012). However, there are some challenges, such as efficient and cost-effective measures, that need to be considered to establish the screening systems. Furthermore, Taylor and Batey (2012) considered digital retinal imaging as one of the screening choices and underlined five principles of retinal screening. These are

comprised of regular screening assurance, the availability of an efficient screening system, eye screening practise being included as part of diabetes care, the ophthalmologist's participation in the planning and operation of the screening system and finally, the quality control of the screening process. Scanlon and colleagues (2009) recommended four steps in systematic screening programmes developed for the sight-threatening diabetic retinopathy. Firstly effective treatment, opportunistic as well as systematic screening, and finally, full quality assurance and coverage screening. Meanwhile, Hutchins et al. (2012) presented a study of diabetic retinopathy screening in New Zealand, and concluded that among the requirements in improving the retinal screening quality should be quality data and quality assurance platforms.

As discussed in Chapter 1, there are many screening methods available for diabetic retinopathy screening. Figure 2.8 shows the screening modalities used in screening programmes including the direct ophthalmoscope, the slit-lamp biomicroscopy with contact lens, the binocular indirect ophthalmoscopy and the fundus photography. However, different screening modalities will provide a variation in the sensitivities and specificities obtained.

Table 2.2 describes the diagnostic accuracy of different screening tools, which are the direct ophthalmoscope, the slit lamp biomicroscope, the mydriatic fundus camera and also the non-mydriatic fundus camera. It can be concluded from Table 2.2, that the non-mydriatic fundus camera has high sensitivity and specificity, eliminating the need for pupillary dilatation, promoting compliance, efficiency and safety. The clinical practice guidelines for the screening of diabetic retinopathy (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine Malaysia, 2011) recommend that the non-mydriatic fundus camera should be used as a screening tool for diabetic retinopathy, whenever possible with a double field fundus photo assessment. When there is no access to a fundus camera, an ophthalmoscope should be used.

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Direct ophthalmoscope	Slit-lamp biomicroscopy with contact lens
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Binocular indirect ophthalmoscopy	Fundus photography

Figure 2.8 Diabetic retinopathy screening tools (Ministry of Health Diabetic Retinopathy Screening Team, 2012c:14)

Table 2.2 Sensitivity and specificity of diabetic retinopathy tools (Ministry of Health Malaysia, Malaysia Society of Ophthalmology and Academy of Medicine of Malaysia, 2011)

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Generally, in current practice, all registered diabetic patients will first undergo the visual acuity test. Following this, fundus photography session will be organised using the fundus camera and assessment will then be performed. A trained paramedic will play a role in grading the captured fundus images into a diabetic retinopathy stage, based on the changes or abnormalities shown on the fundus images. The management of the condition, including a follow-up schedule or referral to an ophthalmologist for further diagnosis, will be decided upon based on the retinopathy stages. This explanation of the diabetic retinopathy screening process is illustrated in Figure 2.9.

Currently in Malaysia, the clinicians use the non-mydratic fundus camera to capture retinal images. The fundus camera comprises an internal or external digital camera, a computer and a software system. It is used because of its strengths as it is easy to use, patient-friendly, user-friendly, time and cost effective and also pupil dilatation is performed only if necessary. The fundus camera produces high quality digital photographs that can be viewed immediately and shown to the patients to improve their understanding of the disease. A fundus camera is designed to photograph the interior surface of the eye such as the retina, the optic disc, the macula, and the posterior pole (i.e., the fundus). Fundus cameras are used by optometrists, ophthalmologists, and trained medical professionals in order to monitor the disease progression, for the diagnosis of a disease or in screening programmes, where the photos can be analysed later.

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Figure 2.9 Screening process of diabetic retinopathy to prevent blindness (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine of Malaysia, 2011)

The handbook or guide to diabetic retinopathy screening by the Ministry of Health Diabetic Retinopathy Screening Team (2012b) explains the technique of photography and also details the features of diabetic retinopathy, visible through the use of the fundus camera. The screening group suggested that two photographs of two views (with the optic disc as the centre and the fovea as the centre) should be taken as the input for

screening, as presented in Figure 2.10. The optic disc or the optic nerve is a round area in the back of the eye while the fovea is the centre of the macula region. Figure 2.11 presents good quality fundus photos, which are essential for the process of diabetic retinopathy screening.

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<tr><td>Optic disc as the centre</td><td>Fovea as the centre</td></tr>
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Figure 2.10 Fundus camera photography (Ministry of Health Diabetic Retinopathy Screening Team, 2012b, 2012d)

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Figure 2.11 Good quality fundus photos (Ministry of Health Diabetic Retinopathy Screening Team, 2012b)

The fundus image can be divided into four quadrants which are superonasal, inferonasal, superotemporal and inferotemporal, as shown in Figure 2.12. The macula region is at the posterior pole of the eye, within one disc diameter of the fovea (Taylor and Batey, 2012).

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Fundus image quadrants	Macula

Figure 2.12 Normal fundus image (Ministry of Health Diabetic Retinopathy Screening Team, 2012b)

2.5.1 Diabetic Retinopathy Grading

Based on the fundus image captured by the fundus camera, the experienced paramedic will then make the diagnosis as to whether or not the patient has any eye disease, including diabetic retinopathy. The grading is performed manually by the paramedics, with reference to any changes or abnormality seen on the retinal image. Table 2.3 shows the findings of diabetic retinopathy features for each stage of the condition. The presented retinopathy stages are the non-proliferative diabetic retinopathy (mild, moderate and severe), the proliferative diabetic retinopathy, the diabetic maculopathy (mild, moderate and severe) and the advanced diabetic eye disease. Information about the retinopathy stages and the terminology used to describe their features of are presented in Section 2.4 and Table 2.1, respectively, for a detailed explanation.

Table 2.3 Retinopathy stages and findings (Ministry of Health Diabetic Retinopathy Screening Team, 2012b)

Retinopathy Stages and Findings	
Mild NPDR	
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oane	
Moderate NPDR	
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Severe NPDR	
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Table 2.3 (continued)

Retinopathy Stages and Findings	
Proliferative DR	
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Diabetic Maculopathy	
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er s	
Mild Maculopathy	
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Table 2.3 (continued)

Retinopathy Stages and Findings	
Moderate Maculopathy	
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Severe Maculopathy	
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Advanced Diabetic Eye Disease	
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The Early Treatment Diabetic Retinopathy Study (ETDRS) group initially proposed the diabetic retinopathy severity scale (Early Treatment Diabetic Retinopathy Study Research Group, 1991). In addition to the early classification by ETDRS, an international clinical disease severity scale for diabetic retinopathy and diabetic macula oedema (DME) was proposed by Wilkinson and others in 2003. It is much simpler, having less severity levels and diagnostic criteria as compared to the ETDRS classification system. Table 2.4 shows the Diabetic Retinopathy Disease Severity Scale including no apparent retinopathy, nonproliferative diabetic retinopathy (mild, moderate and severe) and proliferative diabetic retinopathy. Table 2.5 shows the Diabetic Macular Edema Disease Severity Scale proposed by Wilkinson and colleagues (2003), which has been used as an international scale in order to assist in the grading of fundus images into distinct categories based on the retinal findings.

Table 2.4 International Clinical Diabetic Retinopathy Disease Severity Scale (Wilkinson et al., 2003)

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Table 2.5 Diabetic Macular Edema Disease Severity Scale (Wilkinson et al., 2003)

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2.5.2 Examination Schedule

Regular screening is important for early detection and early treatment, in order to assist the management of diabetic retinopathy. The preliminary fundus examination for diabetic retinopathy varies according to the types of diabetes mellitus, and is presented in Table 2.6 below.

Individuals with diabetes mellitus should be screened at least every two years. Individuals who can be categorised as high risk (i.e. with a longer duration of diabetes or poor control of blood sugar, blood pressure or serum lipid) should be examined at least annually. Moreover, individuals with any signs of non-proliferative diabetic retinopathy should be examined at 6-12 monthly intervals. Earlier follow-up may be required in high risk groups, including the presence of renal complications and the progression of diabetic retinopathy. Table 2.7 provides the recommendations for eye examination follow-up schedules for patients with diabetes mellitus.

Table 2.6 Timing of the first screening (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine of Malaysia, 2011)

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Table 2.7 Recommended follow-up schedule (American Academy of Ophthalmology Retina Panel, 2008)

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The crucial aim for diabetic retinopathy screening is to detect sight threatening factors and to ensure their timely treatment in order to prevent vision loss. Therefore, appropriate referral to an ophthalmologist should be performed. Among the criteria which would require referral are the presence of any level of diabetic maculopathy, severe NPDR, any PDR, unexplained loss of vision and also if the screening examination cannot be performed with an upgradable fundus photo. The National Institute for Clinical Excellence (NICE) presents the urgency of referral as shown in Table 2.8. It is recommended that the examination schedule and urgency of referral to an ophthalmologist should be based on the grade and severity of the diabetic retinopathy along with the presence of risk factors (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine of Malaysia, 2011).

Table 2.8 Criteria for urgent referral (National Institute for Clinical Excellence, 2002)

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2.5.3 Diabetic Retinopathy Management and Treatment

Early detection of diabetic retinopathy is vital because diabetic retinopathy is irreversible. The standard practice for treating diabetic retinopathy is by using laser photocoagulation, where the blood capillaries immersed the energy. The summary of the treatment for diabetic retinopathy is presented in Table 2.9.

Table 2.9 Summary of treatment for diabetic retinopathy (Ministry of Health Malaysia, Malaysian Society of Ophthalmology and Academy of Medicine of Malaysia, 2011)

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2.6 Diabetic Retinopathy Image Processing

Currently, image processing techniques are widely used as a means of diagnosing diseases, including eye diseases. Computer-based imaging tools are necessary to effectively detect signs of diabetic retinopathy. Early detection would allow the ophthalmologist to treat patients before major damage occurs and would present the best chance of protecting the patient's vision. The automatic diabetic retinopathy grading system would allow a faster and more efficient diagnosis. Preventive actions could be taken early to protect vision and avoid blindness.

Diabetic retinopathy screening is currently a common research area, in which some researchers focus on finding and proposing several techniques or methods for detecting certain features of diabetic retinopathy (i.e., microaneurysms, haemorrhages, exudates, and neovascularisation). Nonetheless, there are some researchers who propose the development of automated systems for detecting and classifying normal or abnormal diabetic retinopathy.

Digital image processing systems generally have three main parts: image preprocessing, feature extraction and classification.

2.6.1 Image Preprocessing

Preprocessing is the process of enhancing or improving features of image data for the next processing task. According to Sonka and colleagues (2008), image preprocessing methods can be classified into four categories: pixel brightness transformations, geometric transformations, local preprocessing and image restoration. However, some papers classify image preprocessing methods into image enhancement and image restoration only.

Pixel brightness transformations deal with pixel brightness, and consist of brightness corrections and greyscale transformations. The brightness of pixel is adjusted in brightness correction according to the current brightness and image location; whereas in greyscale transformation, the brightness values contrast of the image is enhanced. The greyscale image is defined as a data matrix which the values are indicated by the shades

of grey (Gonzalez et al., 2009). Sonka and others (2008) concluded that greyscale transformations are mainly used for manual viewing in which the image is simply defined in an improved contrast. For example, greyscale transformation provides a clear contrast to an X-ray image. Greyscale transformation technique includes histogram equalisation for enhancement of contrast. The technique creates an equal distribution of brightness level for the image.

Geometric transformations offer the removal of geometric misrepresentation that happens during the image capturing process. The two basic steps of a geometric transform are pixel coordinate transformation and brightness interpolation. In addition, a significant purpose of image restoration methods, are to subdue degradation. The image restoration methods apply the concept of deconvolution across the whole image.

Local preprocessing methods utilise a small pixel neighbourhood in order to generate an output image with a new brightness value. Two common groups are used to achieve this, namely smoothing and edge detection. Smoothing is used to reduce noise or other minor fluctuations in the image. Gradient operators determine edges where the locations undergo fast changes. There are two components of edge detection, which are magnitude and direction. Most gradient operators such as Roberts, Laplace, Prewitt, Sobel, Robinson and Kirsch can be expressed using convolution masks.

Amongst the preprocessing techniques used in the present diabetic retinopathy detection system are greyscale conversion, green channel extraction, contrast enhancement (such as histogram equalisation), filtering, morphological operations, segmentation and thresholding among others. Within the scope of diabetic retinopathy detection, optic disc elimination and blood vessel removal are two main processes that are widely used as an additional stage, before the next process is performed. In addition, the localisation of the fovea and macula are important for the detection of maculopathy. This detection of these retinal structures also requires some preprocessing techniques. Table 2.10 lists the preprocessing techniques which have been implemented in diabetic retinopathy detection research.

Table 2.10 Summary of preprocessing techniques used in diabetic retinopathy screening research

Authors (Publication year)	Features	Preprocessing techniques
Adal K. M et al. (2014, 2013)	Microaneurysms	Contrast enhancement (Singular Value Decomposition)
Ahmad F. M. H et al. (2007)	Blood vessels	Mean filter, contrast limited adaptive histogram equalisation, bottom-hat morphological transformation
Akram M. U et al. (2013a)	Neovascularisation	Binary mask for background and noisy areas
Akram M. U, Khalid S and Khan S. A (2012)	Microaneurysms	Mathematical morphological operations, contrast normalisation, filter banks, blood vessel enhancement and segmentation
Akram M. U et al. (2014)	Microaneurysms, haemorrhages, exudates	Background separation (mean and variance-based method), blood vessel segmentation (Gabor wavelet and multi-layered thresholding), optic disc extraction (averaging filter and finding the circular region with the maximum intensity values)
Akram M. U, Jamal I, Tariq A and Imtiaz J (2012)	Neovascularisation	Gabor wavelet, multilayered thresholding
Alipour S. H. M et al. (2012)	Exudates, microaneurysms, optic disc, blood vessels	Contrast limited adaptive histogram equalisation, illumination equalisation, morphological operators
Al-Rawi M et al (2007)	Blood vessels	Matched filter
Antal B and Hajdu A (2013, 2010)	Microaneurysms, optic disc, blood vessels	Background subtraction of retinal blood vessels, Walter-Klein contrast enhancement, contrast-limited adaptive histogram equalisation, grey-world normalisation, histogram equalisation, intensity adjustment, vessel removal and interpolation
Aravind et al. (2013)	Microaneurysms, optic disc, blood vessels	Green channel extraction, histogram equalisation, median filter, contrast enhancement, morphological operations
Bala M. P and Vijayachitra S (2012)	Exudates, optic disc	Green channel extraction, histogram equalisation, contrast enhancement, morphological operations
Chowriappa D et al. (2013)	Maculopathy	Colour normalisation, median filter, histogram specialisation, greyscale conversion
Esmaeili M et al. (2013)	Exudates, optic disc	Contrast enhancement, digital curvelet transform (DCUT)

Table 2.10 (continued)

Authors (Publication year)	Features	Preprocessing techniques
Fleming A. D et al. (2006)	Microaneurysms	Green plane, median filter, Gaussian filter, normalisation
Harangi B et al. (2012)	Exudates	Elimination of the optic disc, green channel, Hue, Saturation and Intensity (HSI) colour space, contrast-limited adaptive histogram equalisation, greyscale
Hassan S. S. A and et al. (2011)	Neovascularisation	Colour normalisation, contrast enhancement using sigmoid function, blood vessel extraction
Hatanaka Y et al. (2012)	Microaneurysms	Brightness correction, gamma correction, histogram expansion, green channel extraction, low-pass filter based on Fast Fourier Transform, double-ring filter
Hipwell et al. (2000)	Microaneurysms	Shade-corrected, vessels removal
Hunter A et al. (2011)	Fovea, macula	Contrast enhancement, thresholding, fuzzy c-means region growing, filtering
Jaafar H. F et al. (2010)	Exudates	Morphological top-hat operator, median filtering, shade correction
Jimenez S et al. (2011)	Microaneurysms	Green channel inversion, high pass filtering, contrast enhancement, tophat filtering
Joshi S and Karule P. T (2012)	Blood vessels	Greyscale and green channel conversion, contrast enhancement using contrast-limited adaptive histogram equalisation, image segmentation using morphological operations
Kose C et al. (2012)	Hard exudates, cotton wool spots, microaneurysms, haemorrhages	Extracting the extended background image and determining low and high intensity regions, segmenting bright lesions by applying the inverse adaptive region growing method, segmenting dark lesions, eliminating the optic disc and vessels
Lazar I et al. (2010)	Microaneurysms	Green channel extraction, adaptive thresholding
Lichode R. V and Kulkarni P. S (2013)	Microaneurysms, exudates, blood vessels	Green channel, greyscale conversion, optic disc and blood vessel detection with morphological image processing and image segmentation, Canny edge
Martins C. I. O et al. (2010)	Microaneurysms, blood vessels	Green channel extraction, shade correction
Mizutani et al. (2009)	Microaneurysms, blood vessels	Brightness correction, gamma correction, contrast enhancement, double-ring filter
Mookiah M. R. K et al. (2013)	Normal and DR stages (NPDR and PDR)	Lab colour space, Wiener filtering, grey level shading correction using low pass filtering

Table 2.10 (continued)

Authors (Publication year)	Features	Preprocessing techniques
Nagaveena et al. (2013)	Blood vessels	Green colour plane, adaptive median thresholding
Niemeijer M et al. (2005)	Red lesions	Green plane, spencer frame (shade corrected), bright lesion removal
Osareh A et al. (2003)	Exudates	Normalisation, local contrast enhancement, fuzzy c-means clustering
Prakash J and Sumanthi K (2013)	Microaneurysms	Contrast limited adaptive histogram equalisation, shade correction
Priya R and Aruna P (2012, 2011)	NPDR and PDR	Greyscale conversion, adaptive histogram equalisation, discrete wavelet transform, Gaussian matched filter response, fuzzy c-means clustering
Priya R and Aruna P (2013a)	Haemorrhages, exudates	Greyscale conversion, adaptive histogram equalisation, discrete wavelet transform, matched filter response, fuzzy c-means clustering, green component, thresholding, morphological processing
Priya R et al. (2013b)	Normal and DR (NPDR and PDR)	Greyscale extraction, adaptive histogram equalisation, discrete wavelet transform, matched filter response, fuzzy c-means segmentation
Punnolil A (2013)	Optic disc, fovea, macula, exudates, haemorrhages, microaneurysms	Green channel, greyscale conversion, colour normalisation, morphological image processing
Quellec G et al. (2009)	Microaneurysms	Optimal wavelet transform
Ravishankar A et al. (2009)	Exudates, microaneurysms, haemorrhages, optic disc, blood vessels	Green channel, morphological operations (closing operation, dilation operation, filling operation)
Saleh M. D and Eswaran C (2012)	Microaneurysms, haemorrhages	Green-channel extraction, optic disc removal, background normalisation
Sanchez C. I et al. (2009)	Microaneurysms	Normalisation, mixture model-based clustering
Selvathi D et al. (2012)	Blood vessels, hard exudates, microaneurysms	Discrete curvelet transform, green channel, median filtering, morphological reconstruction, Kirsch's edges, adaptive histogram equalisation, morphological operators
Shome S. K and Vadali S. R. K (2011)	NPDR and PDR	Contrast-limited adaptive histogram equalisation, median filtering

Table 2.10 (continued)

Authors (Publication year)	Features	Preprocessing techniques
Siddalingaswamy P. C and Prabhu K. G (2010)	Optic disc, macula, exudates	Green plane, clustering, mathematical morphological, thresholding
Sopharak A and Uyyanonvara B (2006)	Exudates, optic disc	Hue, Saturation and Intensity (HSI) colour space, median filtering, contrast-limited adaptive histogram equalisation, morphological operators
Sopharak A and Uyyanonvara B (2007)	Exudates, optic disc, blood vessels	Hue, Saturation and Intensity (HSI) colour space, contrast-limited adaptive histogram equalisation, median filtering, fuzzy c-means clustering
Sopharak A et al. (2007)	Exudates	Hue, Saturation and Intensity (HSI) colour space, median filtering, contrast adaptive histogram equalisation, fuzzy c-means clustering, morphological reconstruction
Sopharak A et al. (2009a, 2009b, 2008)	Exudates, optic disc	Hue, Saturation and Intensity (HSI) colour space, median filtering, contrast-limited adaptive histogram equalisation
Sopharak A et al. (2010)	Exudates	Greyscale conversion, median filtering, contrast-limited adaptive histogram equalisation
Sopharak A et al. (2013)	Microaneurysms	Shade correction, median filter, adaptive histogram enhancement vessel detection, optic disc detection
Streeter L and Cree M. J (2003)	Microaneurysms	Green plane, shade correction subtractive or divisive, top hat vessel removal, matched filter, threshold
Sujithkumar S. B and Vipula S. (2012)	Microaneurysms	Green component, greyscale conversion, normalisation (median filter), adaptive histogram equalisation, binarisation (multi-level thresholding), blood vessel removal
Sundhar C and Archana D. (2014)	Exudates, microaneurysms, blood vessels	Green channel and greyscale conversion, normalisation, adaptive histogram equalisation, binarisation
Tariq A et al. (2013)	Optic disc, macula, exudates	Mean and variance-based segmentation, ratio of intensity channel, morphological closing, adaptive contrast enhancement, Gabor kernel-based filter bank, adaptive threshold
Verma K et al. (2011)	Blood vessels, haemorrhages	Matched filter
Vidyasari R et al. (2011)	Microaneurysms, optic disc	Vesselness filter

Table 2.10 (continued)

Authors (Publication year)	Features	Preprocessing techniques
Vimala A. G. S. G and Kajamohideen S (2014)	Macula, exudates	Green component extraction, median filtering, adaptive histogram equalisation, morphological operations
Walter T and Klein J. –C (2002)	Microaneurysms	Grey level transformation, Gaussian filter
Walter T et al. (2007)	Microaneurysms	Polynomial contrast enhancement, contrast enhancement and shade correction
Wisaeng K et al. (2013, 2012)	Exudates	Colour normalisation, local contrast enhancement, median filtering, colour space selection (LUV colour space), optic disc localisation
Wisaeng K et al. (2014)	Optic disc	Colour normalisation, contrast enhancement, median filter, LUV space, morphological method, Otsu's algorithm
Yadao P et al. (2014)	Blood vessels	Mean filtering, Laplacian filtering, contrast function, morphological opening, Gaussian matched filter, thresholding, Kirsch matched filter
Zhang X and Chutatape O (2005)	Haemorrhages	Colour normalisation
Zhang et al. (2009)	Red lesions	Multiscale correlation filtering (MSCF) and dynamic thresholding
Zhang B, Zhang L, Zhang L and Karray F (2010)	Blood vessels	Matched filter with first-order derivative of the Gaussian (MF-FDOG)
Zohra B. F et al. (2009)	Blood vessels, hard exudates	Morphological image processing

2.6.2 Feature Extraction

After performing the preprocessing techniques, feature extraction normally takes place in order to obtain the features from the preprocessed images. Feature extraction in an image processing area helps to detect and separate numerous features of a digitised image as well as video. Basic features extracted for diabetic retinopathy (DR) detection system include area, mean and standard deviation of on pixels (Priya et al., 2011). In addition, there are many feature values used in the DR detection process, namely, the radius of a circle, its diameter, area, perimeter, compactness, aspect ratio, circularity and the pixel's intensity among others. The features can be classified into the shape feature,

intensity feature, colour feature and Fourier descriptor feature. In addition to these types of feature values, there are also features based on texture analysis such as entropy, contrast, homogeneity, correlation, energy which is extracted from the grey level co-occurrence matrix, which can be used to detect DR severity. Table 2.11 presents features value used in previous diabetic retinopathy detection research.

Table 2.11 Summary of feature extraction methods used in previous diabetic retinopathy screening research

Authors (Publication year)	Retinopathy Features	Feature values
Akram M. U et al. (2013)	Neovascularisation	Area, energy, mean gradient, standard deviation gradient, mean intensity, intensity variation, vessels segments, blood vessel density, vascular segment width, vascular direction variation
Akram M. U, Khalid S and Khan S. A (2012)	Microaneurysms	Area, eccentricity, perimeter, compactness, aspect ratio, mean and standard deviation of all green channel pixels, mean and standard deviation of contrast enhanced green channel pixels, mean gradient magnitude value for boundary pixels of candidate lesion, mean gradient value of neighbour pixels in a square region outside the candidate region, mean Hue, Saturation and Value (HSV), standard deviation HSV, entropy, energy, homogeneity, third moments value of all pixels in the square region
Akram M. U et al. (2014)	Microaneurysms, haemorrhages, exudates	Area, eccentricity, perimeter, mean intensity, aspect ratio, compactness, mean HSV, mean enhanced intensity, mean gradient magnitude, mean box gradient, third moment, entropy, mean range filter, energy
Alipour S. H. M et al. (2012)	Exudates, microaneurysms, optic disc, blood vessels	Area, circularity, total number of microaneurysms, total area of exudates, area of blood vessels
Aravind et al. (2013)	Microaneurysms, optic disc, blood vessels	Area, entropy, correlation, energy, contrast, homogeneity, standard deviation, mean

Table 2.11 (continued)

Authors (Publication year)	Features	Feature values
Bala M. P and Vijayachitra S (2012)	Exudates, optic disc	Exudates area, exudates perimeter, number of exudates patches, statistical features (mean, standard deviation, energy, contrast correlation, homogeneity, entropy, cluster shade, cluster prominence, skewness and kurtosis)
Hipwell et al. (2000)	Microaneurysms	13 measurements of intensity and shape (perimeter length, aspect ratio and circularity)
Martins C. I. O et al. (2010)	Microaneurysms, blood vessels	Area, perimeter, circularity, intensity, mean-intensity
Mookiah M. R. K et al. (2013)	Exudates, blood vessels	Exudates area, blood vessel area, node point count, texture (Local Binary Pattern, Laws Texture Energy), entropy
Nagaveena et al. (2013)	Blood vessels	Area of on pixels, mean, standard deviation, energy
Niemeijer M et al. (2005)	Red lesions	Shape features (area, perimeter, aspect ratio, circularity), pixel intensity features (total intensity in the original green plane image, total intensity in the shade corrected image, mean intensity in the original green plane image, mean intensity in the shade corrected image, normalised intensity in the original green plane image, normalised intensity in the shade corrected image, normalised mean intensity in the original green plane image, normalised mean intensity in the shade corrected image, intensity of the region growing seed in the match filtered image, compactness, difference between the mean pixel values inside the object and mean values in a circular region centred on the object in the red plane, green plane, hue image plane, mean and standard deviation of filter outputs, average value of the absolute difference of the two largest eigenvalues, average output of an iris filter
Osareh A et al. (2003)	Exudates	Mean LUV value inside the region, standard deviation of LUV value inside the region, mean LUV value outside the region, standard deviation of LUV value outside the region, LUV values of region centroid, region size, region compactness, region edge strength

Table 2.11 (continued)

Authors (Publication year)	Features	Feature values
Priya R and Aruna P (2013a, 2012)	Blood vessels, haemorrhages and exudates	Radius, diameter, area, arc length, centre angle, half area
Priya R et al (2013b)	NPDR and PDR	Area, radius, diameter, perimeter, centre angle, arc length, mins of arc, volume, mean, median, variance, standard deviation, skewness
Punnolil A (2013)	Optic disc, fovea, macula, exudates, haemorrhages, microaneurysms	Area calculation, texture features (mean, standard deviation, third moment, entropy, homogeneity)
Selvathi D et al. (2012)	Blood vessels, hard exudates, microaneurysms	Area of blood vessels, area of exudates, area of microaneurysms, contrast, homogeneity, correlation, energy
Sopharak A and Uyyanonvara B (2007)	Exudates, optic disc, blood vessels	Intensity value after preprocessing, standard deviation of intensity, hue and number of edge pixels from an edge image
Sopharak A et al. (2009a, 2009b, 2007)	Exudates	Intensity values after preprocessing, standard deviation of intensity, hue, number of edge pixels from an edge image
Sopharak A et al. (2010, 2008)	Exudates	Pixel's intensity value and standard deviation, pixel's hue, number of edge pixels in a region around the pixel, average intensity of the pixel's cluster, size of the pixel's cluster, average intensity of the pixels in the neighbourhood of the pixel's cluster, ratio between the size of the pixel's cluster and the size of the optic disc, distance between the pixel's cluster and the optic disc, six difference of Gaussian (DoG) filter responses
Streeter L and Cree M. J (2003)	Microaneurysms	Linear discriminant analysis, Fourier descriptor (perimeter, mean, area of the object)
Sujithkumar S. B and Vipula S. (2012)	Microaneurysms	Area, perimeter, circularity
Sundhar C and Archana D (2014)	Exudates, microaneurysms, blood vessels	Major and minor axis, perimeter, circularity, area
Tariq A et al (2013)	Optic disc, macula, exudates	Area, compactness, mean intensity, mean hue, mean saturation and mean value
Verma K et al. (2011)	Blood vessels, haemorrhages	Area and perimeter in each of the R, G, B components of the blood vessels and haemorrhages

Table 2.11 (continued)

Authors (Publication year)	Features	Feature values
Walter T et al. (2007)	Microaneurysms	Number of pixels of the candidate region, circularity, maximal value of the top-hat by diameter, mean value of the top-hat, dynamic, outer mean value, outer standard deviation, inner standard deviation, inner mean value, inner range, outer range, grey level contrast between inner and outer region, colour contrast half-range area
Zhang B et al. (2009) Zhang B, Wu X, You J, Li Q and Karray F (2010)	Microaneurysms	Area, perimeter, aspect ratio, circularity, total intensity in green plane and shade corrected image, average intensity in green plane and shade corrected image, normalised intensity in green plane and shade corrected image, normalised average intensity in green plane and shade corrected image, intensity, compactness, difference between the average pixel values of the candidate and a circular region centred on it in the red channel, green channel, blue channel and hue channel, average Gaussian filter response of green plane image, standard deviation response of green plane image, maximum, minimum and average correlation coefficient of the candidate, major axis length and minor axis length of the candidate
Zohra B. F et al. (2009)	Blood vessels, hard exudates	Area of blood, exudates area, contrast, homogeneity

2.6.3 Classification

Classification algorithms are used to access multiple images of the same physical space (Sonka and Fitzpatrick, 2000). Classification algorithms can be categorised into two classes: supervised or unsupervised. A supervised classifier requires input from the user (typically a set of class samples), for the determination of the data structure from which discriminant functions are derived. On the other hand, unsupervised classifiers depend on cluster analysis to derive the natural structure of the data from the data itself. The following sections describe some frequently used classification and clustering algorithm.

2.6.3.1 Support Vector Machines

Support Vector Machines (SVM) was introduced in 1992 by Boser, Guyon and Vapnikin in COLT-92 (Jakkula, 2008). SVM are a set of related supervised learning methods used for classification and regression. A support vector machine is a classification and regression prediction tool that uses machine learning theory to maximise the predictive accuracy while automatically avoiding the over-fit of the data (Jakkula, 2008). SVMs can be defined as systems which use the hypothesis space of a linear function in a high dimensional feature space. The original support vector classifier was developed for the linear separation of two classes and later this limitation was overcome by allowing non-linearly separable classes, non-separable classes, combining multiple 2-class classifiers to yield multi-class classification and other extensions (Sonka et al., 2008).

An SVM works by finding the best hyperplane which separates all data points, which is where the best hyperplane will have the largest margin between the two classes. The margin is the maximal width of the slab parallels to the hyperplane that has no interior data points. The data points closest to the separating hyperplane are support vectors. Figure 2.13 illustrates the functioning of SVM.

An SVM is a popular technique for data classification. Jakkula (2008) concluded its strengths and weaknesses. The major strength of an SVM is that the training is relatively easy, with no local optimum. In addition, it scales relatively easy to high dimensional data and the trade-off between classifier complexity and error can be controlled explicitly. On the other hand, SVM requires a good kernel function and this is one of its weaknesses (Jakkula, 2008; Burges, 1998). In addition its speed and size are its other limitations, both in training and testing (Burges, 1998).

The SVM has been successfully used for pattern classification problems and is also widely used in medical image processing and analysis. Mookiah and others (2012) proposed data mining techniques for an automated diagnosis of glaucoma using Higher Order Spectra (HOS) and Discrete Wavelet Transform (DWT) features. In this case, a support vector machine classifier is used to identify the glaucoma and normal images automatically and with high accuracy. Priya and Aruna (2011) investigated and

proposed a computer-based system for diabetic retinopathy in identifying normal, NPDR and PDR classes. The proposed system uses colour fundus images, where the features are extracted from the raw image using image processing techniques and fed to a support vector machine for classification. Experimental results show that the classification accuracy can provide an improved result, with a sensitivity of 99.45% and a specificity of 100%.

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Figure 2.13 Basic two-class classifications with Support Vector Machines (The Mathworks, Inc., 2016a)

2.6.3.2 Neural Networks

Neural networks are widely used in application areas such as system identification and control, pattern recognition, medical diagnosis, financial application, data mining, visualisation and many more. One of the main applications of neural networks is classification. A neural network consists of many neurons called units or nodes, each of which performs two functions. Firstly the aggregation of its input from other neurons or the external environment, and secondly, the generation of an output from the aggregated inputs (Er et al., 2003).

According to Er and others (2003), a neural network is characterised by its architecture, or connecting pattern among the neurons, its method of determining the weights of the connections and its activation function. Er and colleagues (2003) also presented biomedical engineering applications using one of the Artificial Neural Network (ANN) paradigms. One of its popular applications is in the classification of breast cancer. Er and others (2003) presented the methods and results of the studies corresponding to extracting rules from a mammography dataset and automatically constructed a fuzzy classifier using the Dynamic Fuzzy Neural Network (D-FNN). This was done in order to classify the two important features in breast cancer diagnosis, which are benign and malignant masses. Lin and other co-workers (2003) proposed a neural networks method to determine the progression of glaucoma based on visual field thresholds and concluded that the progression of glaucoma could be detected from visual field thresholds with a neural network.

Gardner and others (1996) initially developed a screening tool for the automatic detection of diabetic retinopathy using an artificial neural network and comparing the network against the ophthalmologist screening of a set of fundus images. As a result, the network achieved good accuracy therefore the system could be used as an aid to the screening of diabetic retinopathy for diabetic patients. Priya and Aruna (2012) enhanced the computer-based system for diabetic retinopathy in identifying normal, NPDR and PDR classes, by using two types of classifiers: a Probabilistic Neural Network (PNN) and a Support Vector Machine (SVM). The classifiers are described in detail and their performances are compared. As a conclusion, it is shown that, from the results obtained, the SVM model is more effective compared to the PNN. Priya and Aruna (2013a) proposed and compared three models, namely a Bayesian classifier, while maintaining the PNN and the SVM in the developed system. Experimental results show that the SVM outperforms all other models and this proves once again, that the SVM is a better choice in detecting and classifying DR categories. The detection of DR disease and its classification with the help of the Radial Basis Function Neural Network (RBFNN) method has also been proposed in (Priya et al., 2013b). However, the experimental results show that the accuracy of the proposed system is relatively low (76.25%) and it

is recommended that its accuracy could be improved by finding more relevant features and by combining it with other classification methods.

2.6.3.3 Other Classification Methods

Naive Bayes classification is another machine learning technique used for classification purpose. The Naïve Bayes classifier can be used when the features are independent of one another within each class, but it works well in practice even when that independence assumption does not hold (The MathWorks, Inc., 2016b). The classifier works in two steps. In the training step, the method estimates the parameters of a probability distribution from the training samples by assuming that the features are conditionally independent, given the class. The method computes the posterior probability of an unseen test sample belonging to each class in the prediction step. The method later classifies the test sample according to the largest posterior probability.

Decision trees are considered to be one of the most popular approaches for implementing classifiers. A decision tree is a classifier in the form of a tree structure and it classifies instances or examples by starting at the root of the tree and moving through it until a leaf node is reached. Rokash and Maimon (2005) pointed out some advantages of using a decision tree, for example it is easy to follow when compacted, as it is self-explanatory. It can handle both nominal and numeric input attributes, can represent any discrete-value classifier and is also capable of handling datasets with errors and missing values.

In the k-nearest neighbour (k-NN) classifier, the object is classified by a ‘majority vote’ from its neighbours, with the object being assigned to the most common class among its *k* nearest neighbours. K-NN offers several advantages including simplicity, effectiveness, intuitiveness and competitive classification performance and it can handle the noisy training data. However, the limitations of the k-NN method include a poor run-time performance if the training set is large and it is also very sensitive to irrelevant or redundant features because all the features contribute to the similarity and the classification (Imandoust and Bolandraftar, 2013).

Acharya et al. (2011) present an automated diagnosis of glaucoma using texture and higher order spectral features from digital fundus images, using a Support Vector Machine, sequential minimal optimisation, Naïve Bayes and random-forest classifiers to perform supervised classification. Table 2.12 summarises the machine learning techniques used in previous research on diabetic retinopathy classification detection.

Table 2.12 Summary of machine learning techniques for classification used in previous diabetic retinopathy screening research

Authors (Publication year)	Features	Classifiers
Adal K et al. (2013)	Microaneurysms	Support Vector Machine (SVM)
Akram M. U et al. (2013)	Neovascularisation	Multimodel m-Mediods based
Akram M. U et al. (2014)	Microaneurysms, haemorrhages, exudates	Hybrid (Gaussian mixture model, Support Vector Machine, extension of multimodel mediod based)
Alipour S. H. M et al. (2012)	Exudates, microaneurysms, optic disc, blood vessels	Support Vector Machine (SVM)
Aravind et al. (2013)	Microaneurysms, optic disc, blood vessels	Support Vector Machine (SVM)
Chowriappa D et al. (2013)	Maculopathy	Hidden Naïve Bayes, sequential minimal optimization (SMO), tree-based J48
Fleming A. D et al. (2006)	Microaneurysms	k-Nearest Neighbour (kNN)
Harangi B et al. (2012)	Exudates	Naïve-Bayes
Hatanaka Y et al. (2012)	Microaneurysms, blood vessels	Three-layered feed forward network
Hunter A et al. (2011)	Maculopathy	Multilayer perceptron neural networks
Lichode R. V and Kulkarni P. S (2013)	Microaneurysms, exudates, blood vessels	Hybrid multilayer feed forward neural network
Lim G et al (2014)	Microaneurysms, haemorrhages, hard exudates	Convolutional Neural Networks (CNNs)
Martins C. I. O et al. (2010)	Microaneurysms, blood vessels	Multilayer perceptron neural network

Table 2.12 (continued)

Authors (Publication year)	Features	Classifiers
Mookiah M. R. K et al. (2013)	Exudates, blood vessels	Probabilistic Neural Network (PNN), Decision Tree (DT), Support Vector Machine (SVM)
Mizutani et al. (2009)	Microaneurysms, blood vessels	Three-layered feed forward network
Niemeijer M et al. (2005)	Red lesions	k-Nearest Neighbour (kNN)
Osareh A et al. (2003)	Exudates	Three layer perceptron neural network
Prakash J and Sumanthi K (2013)	Microaneurysms	Support Vector Machine (SVM)
Priya R and Aruna P (2013a)	Blood vessels, haemorrhages, exudates	Probabilistic Neural Network (PNN), Bayesian, Support Vector Machine (SVM)
Priya R and Aruna P (2013b)	NPDR and PDR	Radial Basis Function Neural Network (RBFNN)
Punnolil A (2013)	Optic disc, fovea, macula, exudates, haemorrhages, microaneurysms	Support Vector Machine (SVM)
Selvathi D et al. (2012)	Blood vessels, hard exudates, microaneurysms	Support Vector Machine (SVM)
Sopharak A, New K. T, Moe, Y. A, Dailey, M. N and Uyyanonvara B (2008)	Exudates	Naïve Bayes
Sopharak A et al. (2010)	Exudates	Naïve Bayes, Support Vector Machine (SVM), Nearest Neighbour (NN)
Streeter L and Cree M. J (2003)	Microaneurysms	Linear Discriminant Analysis (LDA)
Sundhar C and Archana D. (2014)	Exudates, microaneurysms, blood vessels	Four layer backward propagation artificial neural network
Tariq A et al (2013)	Optic disc, macula, exudates	Gaussian Mixture Model (GMM)
Verma K et al. (2011)	Blood vessels, haemorrhages	Random Forests
Vimala A. G. S. G and Kajamohideen S (2014)	Macula, exudates	Support Vector Machine (SVM)

Table 2.12 (continued)

Authors (Publication year)	Features	Classifiers
Walter T et al. (2007)	Microaneurysms	k-Nearest Neighbour (kNN), Gaussian
Zhang X and Chutatape O (2005)	Haemorrhages	Support Vector Machine (SVM)
Zohra B. F et al. (2009)	Blood vessels, hard exudates	Support Vector Machine (SVM)

2.7 Fuzzy Image Processing

Fuzzy approaches are widely implemented in the image processing system developments reported in the literature, mainly for non-medical images but, in a smaller number of cases, are also used for medical image processing. The fuzzy image processing techniques that can be implemented are fuzzy filtering, fuzzy contrast enhancement, fuzzy image segmentation and fuzzy edge detection.

Fuzzy sets were introduced by Zadeh (1965) where they represent the generality of a crisp set. A fuzzy set is a class of objects with a range of grades of membership (Zadeh, 1965). A membership function assigns a grade of membership (ranging between zero and one) to each object. Fuzzy sets using a membership function in order to assess the membership of an element in a set. In addition, fuzzy logic is suitable for modelling uncertainty.

The difference in the visual properties of an object and its background is referred to as contrast. For fuzzy contrast enhancement, Sheet and others (2010) proposed a novel modification of the brightness preserving dynamic histogram equalisation, called the Brightness Preserving Dynamic Fuzzy Histogram Equalization (BPDFHE). This works to improve brightness preservation and contrast enhancement capabilities, but at the same time reduces computational complexity. The implementation stages of the proposed BPDFHE technique are presented in Figure 2.14. The proposed technique was later tested by Garud et al. (2011) to investigate the suitability of the technique for digital pathology images. BPDFHE is a modification to the Brightness Preserving

Dynamic Histogram Equalization (BPDHE) proposed by Ibrahim and Kong (2007), in which the Gaussian kernel was used for a global image histogram smoothing, followed by the segmentation of the valley regions for dynamic equalisation. However, this technique processes the crisp statistics of digital images to enhance contrast, which suffers from the limitation that it does not take into account the inexactness of grey-values and also that crisp histograms need smoothing for equalisation partitioning. In order to overcome this limitation, the fuzzy histogram is introduced to handle the imprecision in grey levels with the appropriate fuzzy membership function, resulting in there being no missing intensity levels and no random fluctuations. The use of fuzzy statistics has improved the algorithm's performance and improved its ability to preserve brightness and provide better contrast enhancement as compared to BPDHE. The proposed technique shows that it can preserve image brightness better than the histogram equalisation and the other techniques based on contrast limited adaptive histogram equalisation.

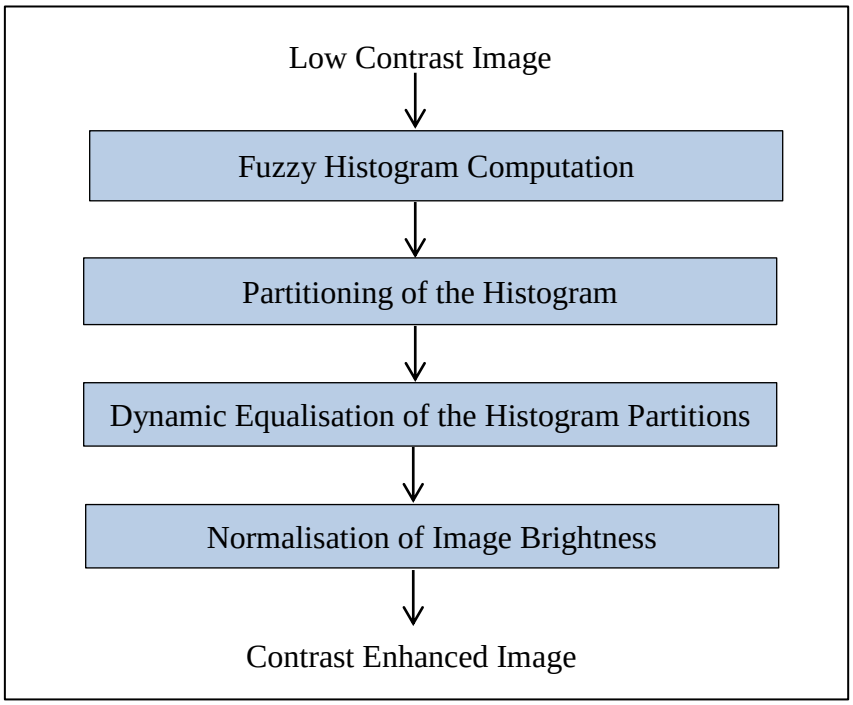

Figure 2.14 Brightness Preserving Dynamic Fuzzy Histogram Equalization stages

Li et al. (2011) proposed a novel fuzzy level set algorithm for medical image segmentation based on the segmentation obtained by spatial fuzzy clustering. The proposed algorithm leads to a better segmentation and effectiveness for medical image segmentation tasks. In addition, fuzzy filter techniques, which aim to detect and remove the noise from the corrupted image, are proposed in (Toh et al., 2010; Kwan et al., 2002; Kwan, 2003; Toh et al., 2008). Toh et al. (2008) proposed a new fuzzy switching median (FSM) filter technique in image processing, which is an extension to the classic switching median filter through employing a fuzzy mechanism in detecting the noisy pixel. The proposed filter was able to effectively remove noise while preserving image details and textures. Later, Toh and others (2010) proposed a novel two-stage noise adaptive fuzzy switching median (NAFSM) filter for the detection and removal of salt-and-pepper noise. The first stage, which is the detection stage, uses the histogram of the corrupted image to identify noise pixels. Meanwhile, the second stage is the noise pixels filtering. After that, fuzzy reasoning is applied to NAFSM filtering in order to handle uncertainty present in the extracted local information. The proposed filter is able to reduce high-density salt-and-pepper noise, as well as preserving fine image details, edges and textures. Kwan (2002, 2003) proposed seven fuzzy filters for noise reduction in images, where the fuzzy filters apply a weighted membership function to an image in order to determine the centre pixel.

Another fuzzy image processing that can be implemented is fuzzy edge detection. An edge is a boundary between two uniform regions. Therefore, the membership functions are defined for fuzzy edge detection to state the degree of a pixel whether it represents an edge or a uniform region. Figure 2.15 shows the membership functions example of the inputs (image gradients) and outputs (intensity of the edge-detected image) for the edge detection, while Figure 2.16 shows the output after the edge detection using fuzzy logic.

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Figure 2.15 Membership functions of the inputs and outputs (The Mathworks, Inc., 2016c)

Original Greyscale Image	Edge Detection Image
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Figure 2.16 Edge detection using fuzzy logic output (The Mathworks, Inc., 2016c)

2.8 Summary

This chapter reviewed the prevalence of diabetes and diabetic retinopathy, including the diabetic retinopathy incidence in addition to the signs and features of diabetic retinopathy. The epidemiology of diabetic retinopathy is also presented to reveal the severity of diabetic retinopathy disease. This chapter also summarised the classification of and screening for diabetic retinopathy, in addition to diabetic retinopathy treatment and the follow up schedule. Image processing was discussed as a tool to diagnose diabetic retinopathy in a more precise and efficient way. At the close of the chapter, background information about digital image processing, image analysis and processing techniques (particularly in diabetic retinopathy detection research) were presented. Finally, fuzzy image processing techniques were also presented.

The summary of preprocessing techniques, feature extractions methods and machine learning techniques for classification used in previous diabetic retinopathy screening research are presented in Table 2.10, Table 2.11 and Table 2.12, respectively. Meanwhile, the fuzzy image processing techniques are presented in Section 2.7. It can be concluded that various image preprocessing techniques, feature extractions and machine learning techniques were proposed in order to produce an efficient and reliable diabetic retinopathy system. The fuzzy image processing techniques help in generating better quality of image and enhanced performance. However, fuzzy processing has not been used during the preprocessing stage for diabetic retinopathy screening system which involves fundus images. Therefore, this proposed research implements fuzzy techniques for the image pre-processing part within the microaneurysms and maculopathy detection.

3 RESEARCH METHODOLOGY AND DATA COLLECTION

This chapter introduces the system design of the proposed research in Section 3.1. Section 3.2 presents the target population involved in the research and the location of the research study in Section 3.3. Section 3.4 explains the types of data collected and the data collection procedure is presented in detail in Section 3.5. An analysis of the data collected is presented in Section 3.6. Alongside the data collection and analysis phase, ethical issues should be considered, which are outlined in Section 3.7. Finally, in addition to the research data set collected, the benchmark public data sets used in the proposed research are presented in Section 3.8 and followed by the summary of the research methodology and data collection chapter in Section 3.9.

3.1 Research Design

Generally, there are six steps in the process of research proposed by Creswell (2012) and they entail: recognising the research problem, review of related literature, specifying a purpose for research, data collection, and analysis and reporting of data, and finally, evaluating the research. Awang (2012) presented a flowchart of research which although similar to Creswell's is more general in its nature.

In general, the data collection techniques for this research project are as follows:

i. Personal interview: face to face informal interviews with the ophthalmologists and trained healthcare staff involve in diabetic retinopathy screening.
ii. Observation: directly observing the process of fundus images capture and its manual grading by trained health care staff.
iii. Internal sources: extracting the existing patient's folder from the personal computer attached to the fundus camera which contains the patient's details, fundus images and diagnosis.

Figure 3.1 presents the research design for the development of this research on 'Automatic Screening and Classification of Diabetic Retinopathy Eye Fundus Images'.

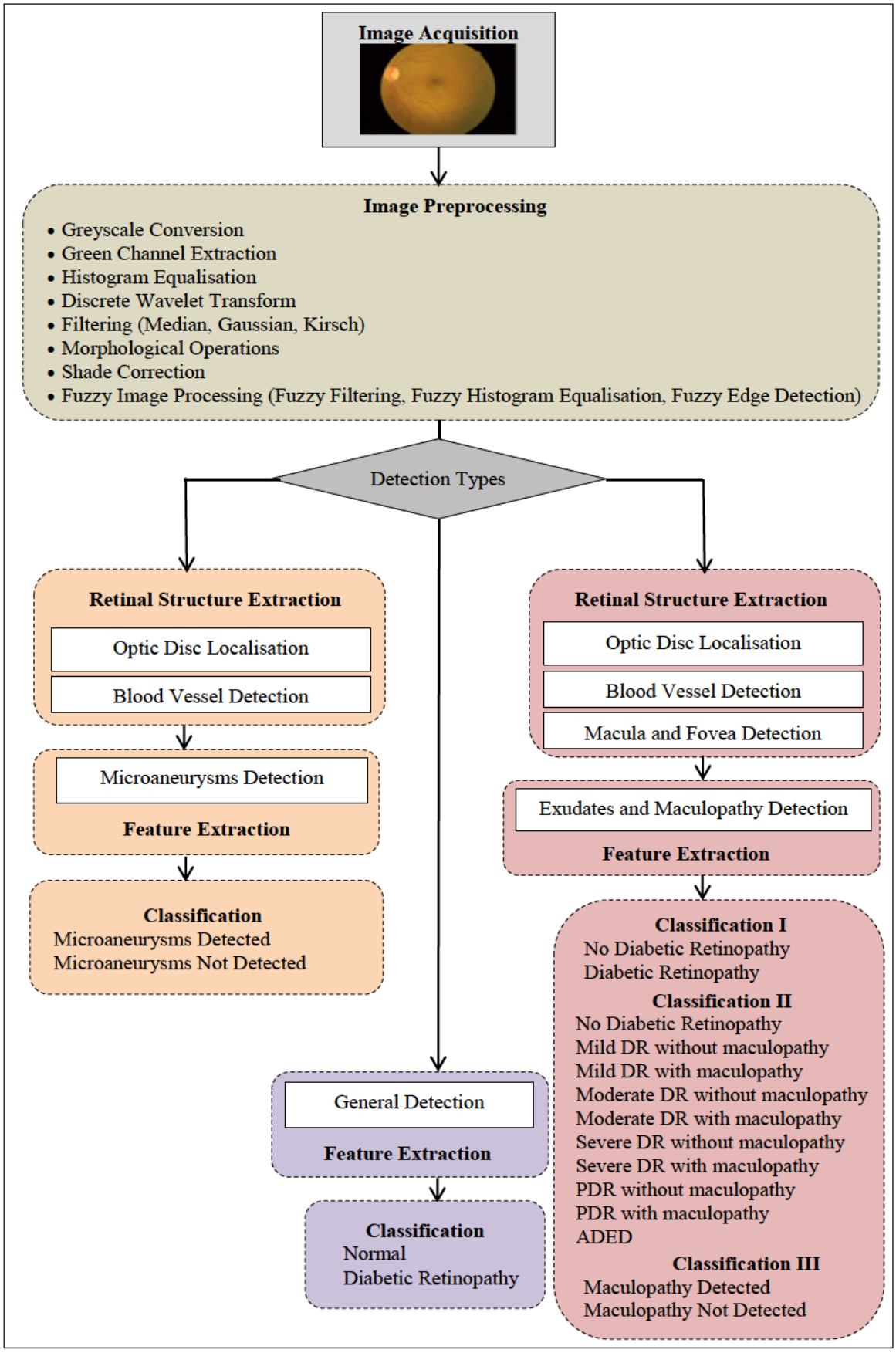

Figure 3.1 Research development design

3.2 Study Population

The study includes both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) patients. It also covers all individuals with diabetes mellitus including adults, children and adolescents. The diabetes mellitus duration is associated to the prevalence of diabetic retinopathy and it varies among nations and ethnicity. Therefore, this study involves individuals from all ethnic groups in Malaysia.

3.3 Location of the Research Study

The study area of Melaka state, is one of the fourteen states that make up Malaysia. The state of Melaka is located in Peninsular Malaysia and is surrounded by Negeri Sembilan, Johor and also the Straits of Malacca. The data is collected from the main hospital in the state of Melaka, the Melaka Hospital, a government-funded public hospital located at Jalan Mufti Haji Khalil, Melaka, Malaysia. It was chosen because its demographic is diverse in terms of ethnicity-religion and socio-economic groupings in the southern part of Malaysia. Generally, the Melaka Hospital is a referral hub for patients from Melaka health centres in addition to other health centres in the north of Johor and a district in Negeri Sembilan, which is Tampin. Furthermore, very few studies of the prevalence of diabetes mellitus and diabetic retinopathy have been carried out in the state. These have mainly focussed on larger urban areas such as Kuala Lumpur and Putrajaya. Therefore, the study will indirectly reveal the diabetes mellitus and diabetic retinopathy prevalence throughout the Melaka state, in order to bridge the prevalence gap with respect to the diabetes mellitus and diabetic retinopathy epidemiology in Malaysia. Figure 3.2 shows the site of the research: at the Melaka Hospital, Malaysia.

3.4 Data Collection

This section introduces the types of data collected in this research project, which were used to response to the research questions and to achieve the objectives. After defining and identifying the research problem and the research design, the task of data collection took place. The method of data collection to be used for the study deals with two types of data: primary and secondary.

Main entrance of Melaka Hospital	Eye Clinic, Department of Ophthalmology, Melaka Hospital

Figure 3.2 Research study location

3.4.1 Primary Data

Data which is new, original and collected for the first time is termed as primary data (Kothari, 2004). The Social Dimensions of the Watershed Planning (2006) defined primary data as generated and compiled data through interviews, surveys or focus groups. In addition, the Social Dimensions of the Watershed Planning (2006) also claimed that those data types are designed in order to address an unavailable issue or information need in any present sources. Primary data is tailored to provide well-focused and exclusive support for the decision-makers of organisations, but on the other hand, the collection and analysing of the data more expensive and time consuming (Malhotra and Birks, 2006). In order to develop the proposed system for the purpose of this project, primary data which is information gathered from observation and interview, has been collected. The detail of the observation strategy is explained in Section 3.5.1, while the interview strategy is explained in Section 3.5.2.

3.4.2 Secondary Data

Secondary data is defined as data which has been collected by another party and has undergone a statistical process (Kothari, 2004). Secondary data is also classed as data

that has already been collected for some other purpose (Sounders et al., 2009; Malhotra et al., 2006).

According to Sounders et al. (2009), organisations collect and store a diversity of data in order to support their operations. Sounders et al. (2009) highlighted some of the advantages of using secondary data in a research project, and they include having fewer resource requirements, being inconspicuous, being practical for longitudinal studies and offering comparative and contextual data. Sounders et al. (2009) however, also revealed the disadvantages of using secondary data: data collected may not match with need, access can be difficult or costly, in addition to unsuitable aggregations and definitions. The secondary data for this research project however are collected from an internal source, namely fundus images. Section 3.5.3 will describe the details of the secondary data collection method.

3.5 Collecting Data Procedure

The data collection techniques for the primary data are observations and interviews, while the secondary data is collected from existing fundus images.

3.5.1 Collecting Primary Data through Observation

Observation is one of the techniques implemented for this study. According to Sounders et al. (2009), participant observation and structured observation are two types of observation. Sounders et al. (2009) differentiated between the two kinds of observation in which participant observation is qualitative and stresses the discovery of meanings that people attach to their actions. Structured observation however, according to Sounders et al. (2009), is quantitative and is more concerned with the frequency of those actions. Kothari (2004) explained that an observation is defined as information collected by an investigator's own observation without having interviewed the respondents. Kothari (2004) also outlined the disadvantages of the observation method: costs, the provision of limited information and its unsuitability for larger samples.

For the proposed research project, an observation method is used that has a direct understanding of the process by which fundus images involving diabetes mellitus patients are captured using a fundus camera. It also includes the manual grading process of the captured fundus images by trained health care staff during the screenings, as shown in Figure 3.3. The observation is important in order to understand the following: how the fundus camera works, the process of fundus images capture and the manual grading of fundus images, which is aimed to be converted into a fully automated grading process.

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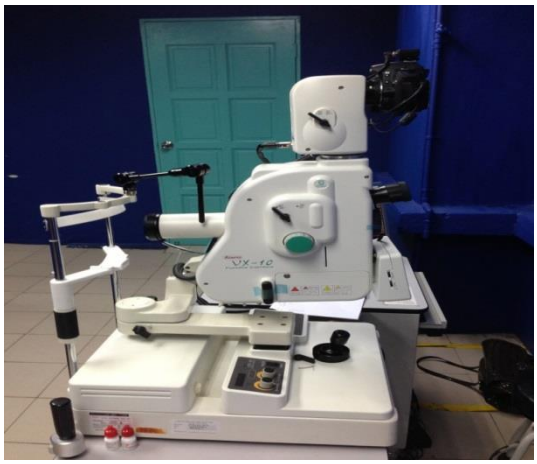
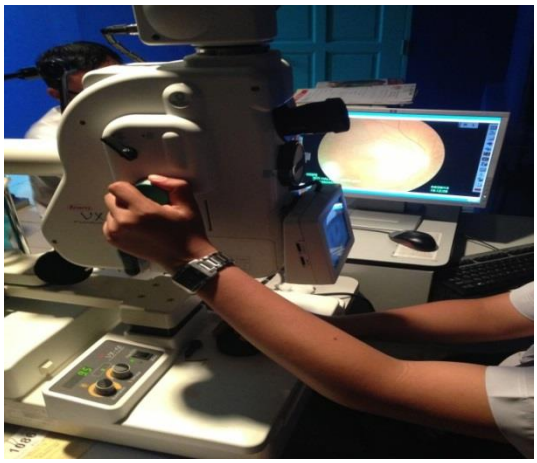
<tr><td>This item has been removed due to Data Protection. The unabridged version of the thesis can be found in the Lancester Library, Coventry University.</td><td>  </td></tr>
<tr><td>Visual acuity test</td><td>Fundus camera KOWA VX-10</td></tr>
<tr><td>This item has been removed due to Data Protection. The unabridged version of the thesis can be found in the Lancester Library, Coventry University.</td><td>  </td></tr>
<tr><td>Fundus camera capture</td><td>Grading process</td></tr>
</table>

Figure 3.3 Fundus images capturing and the grading process

3.5.2 Collecting Primary Data through Interview

According to Kothari (2004), a personal interview session requires the investigator to follow a firm procedure and seek answers to a set of predetermined questions. In additions, Kothari (2004) claimed that an interview is usually performed in an organised manner and the output produced will be determined by the interviewer's capability.

Face to face interviews with an ophthalmologist and a medical assistant involved in the diabetic retinopathy screening are performed for the purposes of this study. A personal interview with the ophthalmologist is required to gather valuable information about the ophthalmology field, specifically on diabetic retinopathy, as well as the features of diabetic retinopathy signs, the diabetic retinopathy screening process and the respective management of patients with diabetic retinopathy problem. In addition, discussion with respect to the ground truth from the collected data is held with more experienced ophthalmologists. The ophthalmologists will determine the types of retinopathy for each of the data examples based on the retinopathy signs found on the fundus images. The produced ground truth is important with respect to the system testing phase, where the manual diabetic retinopathy analysis by several experienced ophthalmologists will be compared to the results of the automated system developed in this research project.

3.5.3 Collecting Secondary Data through Existing Fundus Images

The most important data for this research study are fundus images which are taken from the fundus camera located in the screening room. The fundus images from the diabetic patients are captured by experienced medical staff for screening. For the purposes of this research, numerous clinical fundus retinal images from the personal computer attached to the fundus camera are extracted and analysed. The developed system proposed by this study is tested on both normal and colour fundus images obtained from patients with diabetes mellitus. Manual diabetic retinopathy diagnosis, carried by an experienced paramedic is, then compared to the results of the automated system in order to test and improve the sensitivity and specificity of the proposed grading methods.

3.6 Data Management and Analysis Procedure

The task of data analysis will take place after the data collection phase. This requires several correlated operations, for example the categories establishment and their raw data application such as coding and formulation, followed by statistical inferences (Kothari, 2004).

For this research project, manual analysis by experienced paramedics is compared to the results of the automated system based on the provided ground truth. The sensitivity and specificity are calculated to test the capability of the proposed system and its potential as a quality assurance in retinal screening. Sensitivity is the percentage of abnormal fundus images which have been classified as abnormal, while specificity is the percentage of normal fundus images classified as normal by the screening. Accuracy can also be calculated as a feature of the screening's quality assurance. According to the UK National Institute for Clinical Excellence, well-designed screening studies are required to determine whether new tests of screening or early detection (such as digital camera retinal photography) meet the standards of 80% sensitivity and 95% specificity (National Institute for Clinical Excellence, 2002). Listed below are four possible outcomes of a screening. Results are required in sensitivity, specificity and accuracy calculations (Taylor and Batey, 2012):

i. True negative: the image is normal and was reported by the screener as normal
ii. True positive: the image shows retinopathy and was correctly reported by the screener as having retinopathy
iii. False negative: the image shows retinopathy but was reported by the screener as normal
iv. False positive: the image is normal but was reported by the screener as showing retinopathy

Table 3.1 shows the formula to calculate the sensitivity, specificity and accuracy respectively, as explained above.

Table 3.1 Sensitivity, specificity and accuracy formula

Features	Formula
Sensitivity	$\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}} \times 100$
Specificity	$\text{Specificity} = \frac{\text{True negatives}}{\text{True negatives} + \text{False positives}} \times 100$
Accuracy	$\text{Accuracy} = \frac{\text{True positives} + \text{True negatives}}{\text{True positives} + \text{False positives} + \text{True negatives} + \text{False negatives}} \times 100$

3.7 Ethical Considerations

Ethical conduct should be applied throughout the research work and researchers should observe and follow research ethics at all time. Awang (2012) underlined the basic principles of ethical research that need to be considered, such as harm protection, privacy maintenance, coercion, informed consent, confidentiality and also the sharing of findings.

Creswell (2009) presented ethical issues in more detail by dividing them into issues specifically regarding the research problem, the purpose and questions of the research, ethical issues regarding collection of data, ethical issues about analysis and interpretation of data and finally, the research writing and disseminating ethical issues. According to Bhattacherjee (2012), there are some ethical principles used in scientific research, such as voluntary involvement, informed consent, privacy and confidentiality, disclosure and also ethical principles on analysis and reporting.

In order to conduct this research, an ethical approval was obtained from Coventry University Ethics Committee, where the research risk assessment was performed. The research was categorised as low risk research, where no human participants are directly involved and where only secondary data is used. In addition, as the research involves medical data from Malaysia, ethics approval from the Medical Research and Ethics Committee, Ministry of Health Malaysia has been obtained as a requirement in order to

conduct the research and collect medical data from Malaysian health clinics and hospitals. Patient confidentiality and medical data protection are the important ethical issues that need to be considered in this case.

3.8 Benchmark Public Data Sets

There are several public data sets available for the benchmarking of diabetic retinopathy detection from digital images. In order to run and test the developed system, firstly, fundus images from publicly available data sets will be used as a benchmark before running the system with the fundus images collected from the Melaka Hospital. Some of the most popular public databases which contain eye fundus images are the Standard Diabetic Retinopathy Database Calibration Level 0 (DIARETDB0), the Standard Diabetic Retinopathy Database Calibration Level 1 (DIARETDB1), Methods to Evaluate Segmentation and Indexing techniques in the field of Retinal Ophthalmology (MESSIDOR), Digital Retinal Images for Vessel Extraction (DRIVE), STructured Analysis of the Retina (STARE), the Retinal Vessel Image set for Estimation of Widths (REVIEW) and the Retinopathy Online Challenge (ROC) database.

One of the more popular data sets containing a combination of normal and diabetic retinopathy fundus images is the Standard Diabetic Retinopathy Database Calibration Level 0 (DIARETDB0). The data set consists of 130 colour fundus images of which 20 are normal and the remaining 110 contain signs of diabetic retinopathy, such as hard exudates, soft exudates, microaneurysms, haemorrhages and neovascularisation. The original images, sized 1500 x 1152 in PNG format, are captured with a 50 degree field-of-view digital fundus camera with an unknown camera setting (Kauppi et al., 2006). In addition to the DIARETDB0, there is another data set developed by the Machine Vision and Pattern Recognition Research Group at Lappeenranta University of Technology, Finland, which is the Standard Diabetic Retinopathy Database Calibration Level 1 (DIARETDB1), with 89 colour fundus images, including 84 images with at least mild non-proliferative signs (microaneurysms) of diabetic retinopathy in addition to five normal images (Kauppi et al., 2007).

The methods to evaluate the segmentation and indexing techniques in the field of retinal ophthalmology or the MESSIDOR database is another data set, produced by research funded by the French Ministry of Research and Defence to facilitate studies on diabetic retinopathy diagnosis (Messidor, 2004). It consists of 1,200 colour fundus images captured using a colour video 3CCD camera on a Topcon TRC NW6 non-mydriatic retinograph with a 45 degree field of view. The images acquired by three ophthalmologic departments have three different sizes: 1440 x 960, 2240 x 1488 and 2304 x 1536 pixels and 8 bits colour representation (Messidor, 2004).

Another retinal images database is from the Digital Retinal Images for Vessel Extraction (DRIVE) project, which offers both retinal colour images and the results of the automatic segmentation of blood vessels. The set of 40 images, where 33 do not show any sign of diabetic retinopathy and seven show signs of mild early diabetic retinopathy, are captured using a Canon CR5 non-mydratic 3CCD camera with a 45 degree field of view, 8 bits per colour plane and a size of 768 by 584 pixels (Staal et al., 2004).

The STructured Analysis of the Retina (STARE) project by Dr. Michael Goldbaum at the University of California, San Diego, funded by the U.S. National Institutes of Health, is another database with retinal colour images (Hoover et al., 2003). The set of 400 raw images including a list of diagnosis codes and a diagnosis for each image can be obtained from the STARE database. Blood vessel segmentation work involves 40 of these images (Hoover et al., 2000), while 80 images are used for optic nerve detection (Hoover et al., 2003).

The DRIVE and STARE data set are excellent databases of retinal vessel pixel segmentations; however they do not include width measurements. Therefore, the Retinal Vessel Image set for Estimation of Widths (REVIEW) data set is presented to fill this gap. The data set includes 16 images with 193 vessel segments and a variety of pathologies and vessel types. The database contains accurate width measurements and four subsets of images, which are categorised in four classes: high resolution, vascular disease, central light reflex and kick-points. Al-Diri and others (2008) have described

the REVIEW data set for retinal vessel and the algorithm used to process the segmentation in order to produce vessel profiles.

The Retinopathy Online Challenge (ROC) presents an online competition for numerous methods for the detection of microaneurysms which can be compared using the same data set (Niemeijer et al., 2010). The images have three different sizes: 768 x 576, 1058 x 1061 and 1389 x 1383. The data set consists of 50 training images of colour fundus photographs with available reference standards, and 50 test images where the reference standard was withheld by the organisers. The overall results show that the detection of microaneurysms has been a challenging task for both automatic methods and human expertise.

3.9 Developed Data Set

In addition to the public data sets presented above, a combination of normal and Diabetic Retinopathy (DR) fundus images from a novel data set was developed as part of this research.

The fundus images are collected from the Eye Clinic, in the Department of Ophthalmology, at the Melaka Hospital, Malaysia. The novel data set consists of 600 colour fundus images collected from 300 patient's folders. Each of the patient's folders has a minimum of two images, at least one for the right side and one for the left side, where two different angles were captured; with the optic disc and the macula respectively at the centre. The original images, which are sized 3872 x 2592 in JPEG format, provide high quality and detail. These were captured with a KOWA VX-10 digital fundus camera. Figure 3.4 shows some examples of the images from the new developed data set. Three experts from the Department of Ophthalmology at the Melaka Hospital, Malaysia were involved in order to diagnose the fundus images into ten retinopathy stages: No Diabetic Retinopathy, Mild DR without maculopathy, Mild DR with maculopathy, Moderate DR without maculopathy, Moderate DR with maculopathy, Severe DR without maculopathy, Severe DR with maculopathy, Proliferative DR without maculopathy, Proliferative DR with maculopathy and Advanced Diabetic Eye Disease (ADED). An Excel file containing the link to each eye

fundus image and the retinopathy stages drop down list, as presented in Figure 3.5 was provided to each of the experts separately in order to avoid bias. The summary findings of the three experts are presented in Figure 3.6. The average from the three experts is used for the overall expert diagnosis, as shown in Figure 3.7. As a result of the analysis of the experts' diagnosis, performed using SPSS software, the total number of images in each class is as follows: normal (no retinopathy) class with 276 images, while the abnormal or diabetic retinopathy (DR) class can be divided into nine other categories including mild DR without maculopathy (72), mild DR with maculopathy (27), moderate DR without maculopathy (85), moderate DR with maculopathy (83), severe DR without maculopathy (23), severe DR with maculopathy (11), proliferative DR without maculopathy (6), proliferative DR with maculopathy (10) and, finally, advanced diabetic eye disease, ADED (7). These are presented in Table 3.2. Meanwhile, the data analysis procedures of the novel dataset are discussed in Chapter 5 (Overall Results Analysis and Discussion), together with the system results analysis.

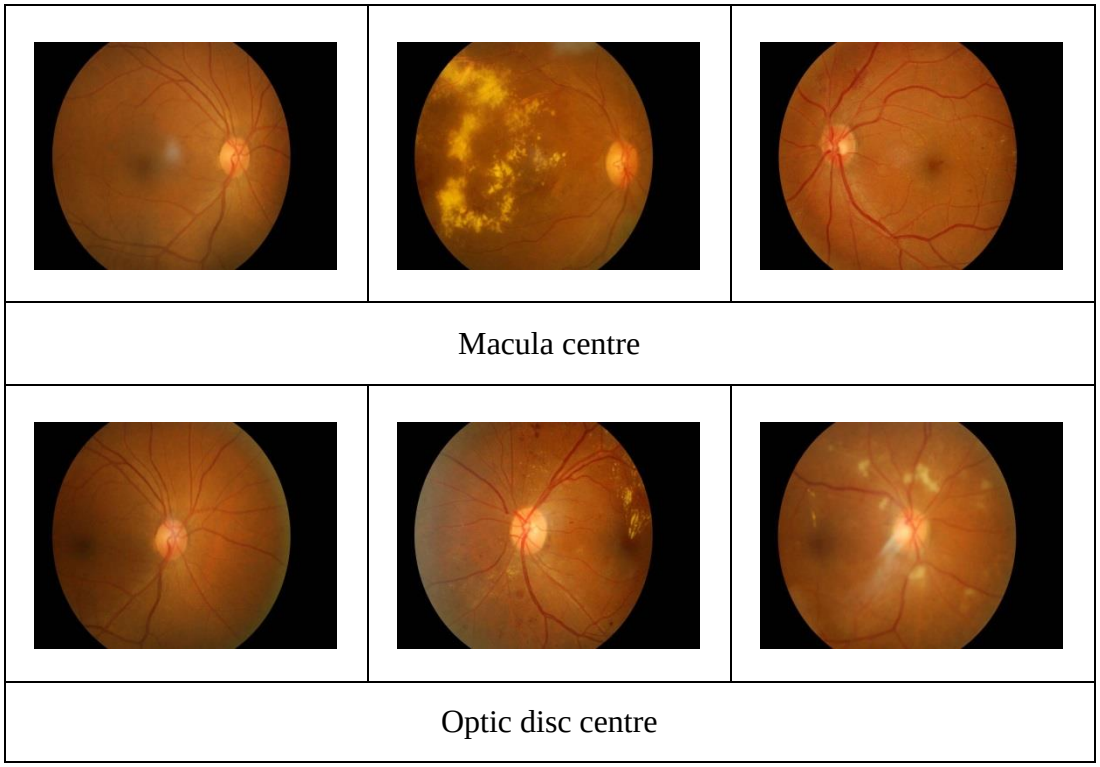
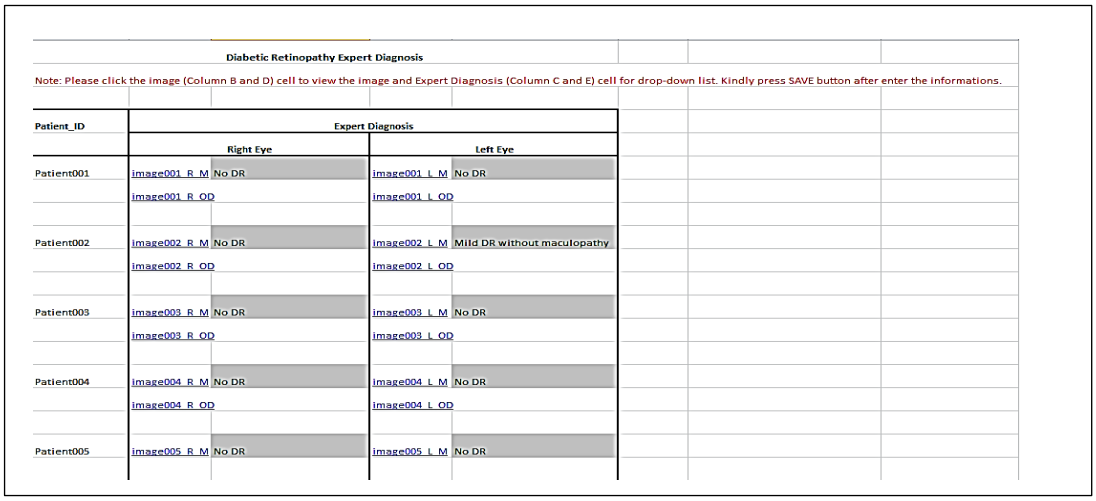


Figure 3.4 Examples of images in the dataset

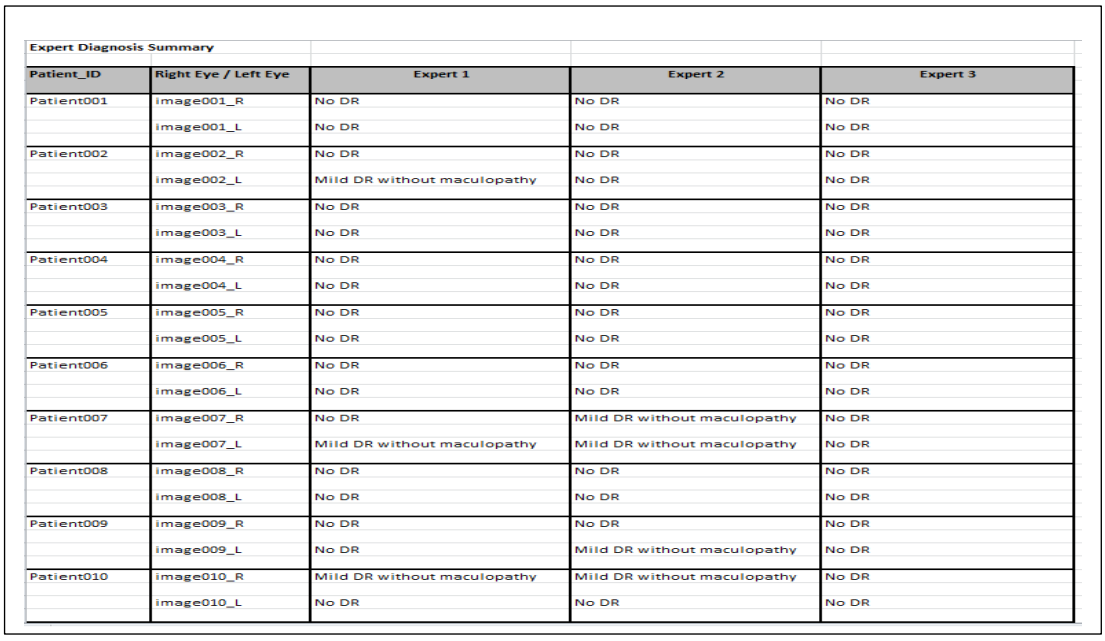


Diabetic Retinopathy Expert Diagnosis

Note: Please click the image (Column B and D) cell to view the image and Expert Diagnosis (Column C and E) cell for drop-down list. Kindly press SAVE button after enter the informations.

Patient_ID	Expert Diagnosis			
	Right Eye		Left Eye	
Patient001	image001_R_M	No DR	image001_L_M	No DR
	image001_R_OD		image001_L_OD	
Patient002	image002_R_M	No DR	image002_L_M	Mild DR without maculopathy
	image002_R_OD		image002_L_OD	
Patient003	image003_R_M	No DR	image003_L_M	No DR
	image003_R_OD		image003_L_OD	
Patient004	image004_R_M	No DR	image004_L_M	No DR
	image004_R_OD		image004_L_OD	
Patient005	image005_R_M	No DR	image005_L_M	No DR

Figure 3.5 Expert diagnosis file



Expert Diagnosis Summary

Patient_ID	Right Eye / Left Eye	Expert 1	Expert 2	Expert 3
Patient001	image001_R	No DR	No DR	No DR
	image001_L	No DR	No DR	No DR
Patient002	image002_R	No DR	No DR	No DR
	image002_L	Mild DR without maculopathy	No DR	No DR
Patient003	image003_R	No DR	No DR	No DR
	image003_L	No DR	No DR	No DR
Patient004	image004_R	No DR	No DR	No DR
	image004_L	No DR	No DR	No DR
Patient005	image005_R	No DR	No DR	No DR
	image005_L	No DR	No DR	No DR
Patient006	image006_R	No DR	No DR	No DR
	image006_L	No DR	No DR	No DR
Patient007	image007_R	No DR	Mild DR without maculopathy	No DR
	image007_L	Mild DR without maculopathy	Mild DR without maculopathy	No DR
Patient008	image008_R	No DR	No DR	No DR
	image008_L	No DR	No DR	No DR
Patient009	image009_R	No DR	No DR	No DR
	image009_L	No DR	Mild DR without maculopathy	No DR
Patient010	image010_R	Mild DR without maculopathy	Mild DR without maculopathy	No DR
	image010_L	No DR	No DR	No DR

Figure 3.6 Expert diagnosis summary

Image_ID	Expert_1	Expert_2	Expert_3	Overall_diagnosis	Average
image001_R	1	1	1	3	1
image001_L	1	1	1	3	1
image002_R	1	1	1	3	1
image002_L	2	1	1	4	1
image003_R	1	1	1	3	1
image003_L	1	1	1	3	1
image004_R	1	1	1	3	1
image004_L	1	1	1	3	1
image005_R	1	1	1	3	1
image005_L	1	1	1	3	1
image006_R	1	1	1	3	1
image006_L	1	1	1	3	1
image007_R	1	2	1	4	1
image007_L	2	2	1	5	2
image008_R	1	1	1	3	1
image008_L	1	1	1	3	1
image009_R	1	1	1	3	1
image009_L	1	2	1	4	1
image010_R	2	2	1	5	2
image010_L	1	1	1	3	1

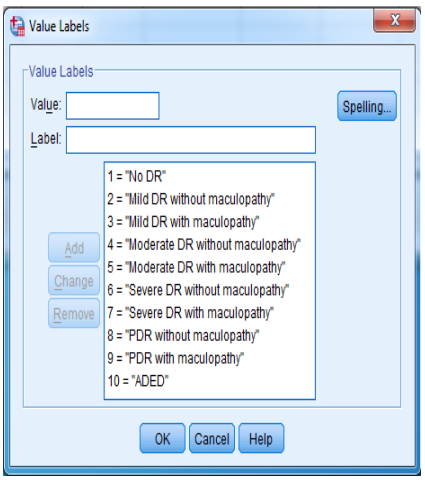


Figure 3.7 Expert diagnosis average

Table 3.2 Expert diagnosis summary

Retinopathy Stage	No. of Images
No DR	276
Mild DR without maculopathy	72
Mild DR with maculopathy	27
Moderate DR without maculopathy	85
Moderate DR with maculopathy	83
Severe DR without maculopathy	23
Severe DR with maculopathy	11
PDR without maculopathy	6
PDR with maculopathy	10
ADED	7
Total	600

The new dataset is different when compared to the other datasets, presented earlier in Section 3.8. The data set represents the South East Asian population, particularly Malaysian, unlike the other datasets, which represent the Caucasian population. It provides an almost balanced total number of No DR/Normal and DR/Abnormal images. Typically, in the diagnosis of medical images, it is difficult to find a large number of normal cases. The imbalanced number of available images poses some problems in the classification phase; therefore, the balanced number in the new dataset will help overcome this problem.

Moreover, the categorisation of the expert diagnosis followed the standard practice based on the International Clinical Retinopathy and Diabetic Macula Oedema Disease Severity Scale. The classification of the data involves maculopathy, which is the yellow lesion near the macula. This is a very detailed categorisation compared to other data sets. The detection of maculopathy is very important, as the macula is responsible for central vision and it represents a sensitive part of the eye. It is vital therefore in detecting the urgency of a referral. In addition, the novel dataset and the expert diagnosis may be used separately for both diabetic retinopathy grading and diabetic maculopathy grading.

In order to make the novel fundus images dataset widely accessible, it has been made available as an online database. The novel dataset is accessible at http://creative.coventry.ac.uk/fundus. The webpage of this research contains the novel dataset with eye fundus images, including the expert diagnosis file and the published papers related to this research project. Figure 3.8 shows the screenshot of the main page of the dataset webpage. The aim of this online database is to highlight the research project development and to promote research on retinal-imaging to enable comparative studies and, most importantly, to share the eye fundus images with other researchers. The dataset can be downloaded for research and educational purposes.

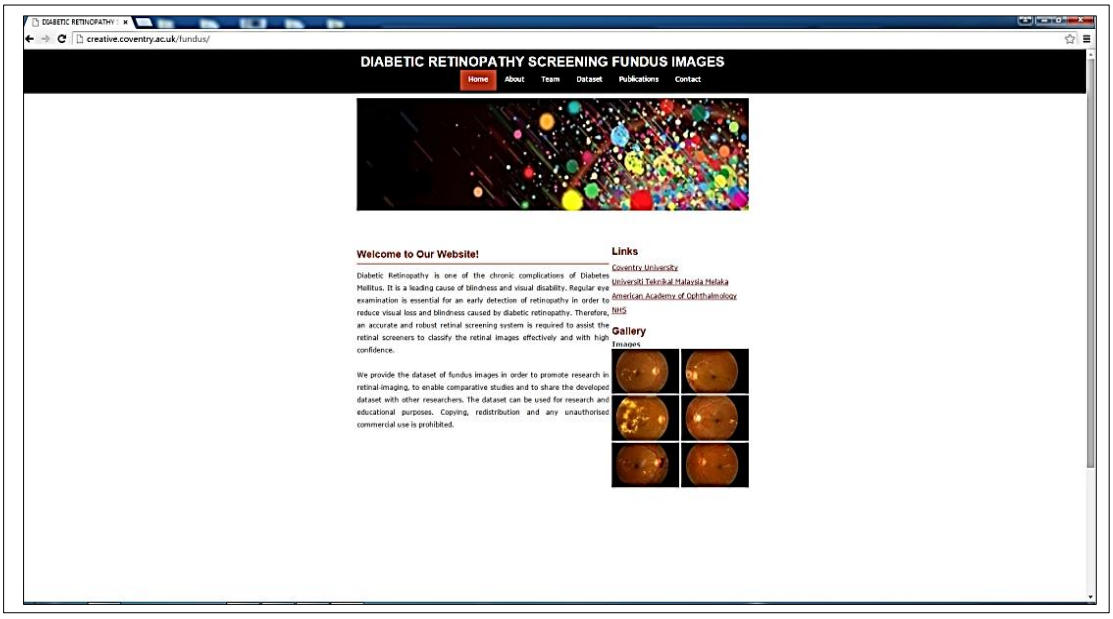


Figure 3.8 Main web page for the developed dataset

3.10 Summary

The chapter discussed the main phases involved in the research development, beginning with the research design outline which implemented in the study. The data collection and analysis are important stages in the research design. In this respect, the data collection instruments were presented focusing on the data collection process design and management. Ethical issues should also be considered in research, when dealing with people and organisations. The chapter also provided information on the ethical considerations involved in this research. Significantly, a high quality of data, i.e., fundus images and adequate techniques, can help rise the quality and efficiency of the developed system, therefore, eye fundus images new dataset which would be beneficial to researchers and practitioners in the area of retinal imaging was introduced, in addition to the other public datasets used for the purposes of evaluation.

Table 3.3 shows a mapping table that lists the datasets used for each system development in this research work. The Standard Diabetic Retinopathy Database Calibration Level 0 (DIARETDB0) is used for the evaluation of System I, while the Standard Diabetic Retinopathy Database Calibration Level 1 (DIARETDB1) is used for System II evaluation. The Retinopathy Online Challenge (ROC) dataset is used for the evaluation of microaneurysms detection in System III and System IV. The new developed dataset collected from Melaka Hospital is used for the evaluation of System VI and System VII, for the maculopathy and diabetic retinopathy detection. In addition to the justification of the datasets used, Table 3.3 provides the type of the system detection.

Table 3.3 Summary of datasets used for systems development

	System I	System II	System III	System IV	System V	System VI	System VII
Dataset Used							
Benchmark Public Dataset:							
- DIARETDB0	√						
- DIARETDB1		√					
- MESSIDOR							
- DRIVE							
- STARE							
- REVIEW							
- ROC			√	√			
Developed Dataset:							
- Melaka Hospital					√	√	√
Type of System Development	General detection	General detection	Microaneurysms detection	Microaneurysms detection	Maculopathy detection	Maculopathy detection	Maculopathy detection
Justification of Selected Dataset	- A combination of normal and diabetic retinopathy fundus images - Suitable for general classification	- Contains normal fundus images and images with mild NPDR - Suitable for general classification	- ROC presents an online competition for numerous methods in microaneurysms detection to compare with each other on the same data - Suitable for the microaneurysms detection and classification		- New dataset consists of 600 fundus images and experts diagnosis which diagnose the fundus images into ten retinopathy stages, following the ophthalmologists practice - Suitable for the maculopathy and diabetic retinopathy detection and classification		

4 CONTRIBUTIONS TO DEVELOPING SYSTEMS FOR DIABETIC RETINOPATHY AND MACULOPATHY DETECTION

Several systems, implementing different methods, have been proposed for diabetic retinopathy screening in the course of this research. The development of the proposed systems can be categorised into three types of approach. The first system development is based on a general detection of diabetic retinopathy (i.e., either normal or with retinopathy present). Meanwhile, the second type presents several system developments for the detection of microaneurysms, an important sign of diabetic retinopathy. Finally, the third type explains the development of two systems in order to detect diabetic retinopathy alongside maculopathy.

This chapter presents the development and evaluation of each of the proposed types of system development. They present a combination of techniques, such as different preprocessing techniques, different feature parameters and different classifiers in a diabetic retinopathy screening system, which differs from systems proposed by other researchers. The preliminary screening system (System I) for the general detection of diabetic retinopathy is presented in Section 4.1. The detection of microaneurysms in colour fundus images is presented in Section 4.2. The first two systems (System II and System III) for the detection of microaneurysms, which highlight the use of feature extraction and classification methods, are explained in Section 4.2.1 and Section 4.2.2, respectively. The other two proposed systems (System IV and System V) for the microaneurysms detection, which implement the fuzzy image processing techniques, are reported in Section 4.2.3 and Section 4.2.4. Section 4.3 presents the two systems (System VI and System VII) for the detection of diabetic retinopathy alongside the detection of maculopathy in the eye's fundus images. Finally, a summary of the chapter is presented in Section 4.4.

4.1 Basic System for General Diabetic Retinopathy Detection (System I)

This section presents a preliminary system for the classification and screening of diabetic retinopathy using eye fundus images. This is a general detection system of diabetic retinopathy that classifies images into two main classes: normal and with diabetic retinopathy. The system is evaluated by using the Standard Diabetic Retinopathy Database Calibration Level 0 (DIARETDB0), described in Section 3.8, which consists of 130 colour fundus images (Kauppi et al., 2006).

The system explored and implemented some basic image processing techniques, which will be used for further developments of the diabetic retinopathy screening system. Rahim and others (2014) reported the development of such an automatic screening and classification of diabetic retinopathy fundus images in detail, while exploring the existing systems and applications related to diabetic retinopathy screening and detection methods. This system is an automatic system for detecting diabetic retinopathy by classifying the images into general detection categories, which are normal (no apparent retinopathy) or abnormal (retinopathy present).

The proposed ophthalmic decision support system consists of an automatic acquisition, screening and classification of diabetic retinopathy fundus images, which will assist in the detection and management of diabetic retinopathy. The developed system contains four main parts, namely the image acquisition, the image preprocessing, the feature extraction, and the classification using several machine learning techniques.

The proposed screening system has been developed using open source software, OpenCV (Open Source Computer Vision) and Microsoft Visual C++ 2010. The OpenCV environment, developed by Willow Garage, is a programming library offered for real time computer vision (Itseez, 2014). OpenCV includes a collection of standardised image analysis and machine vision algorithms to be used by developers. Most work in this area uses tools such as Matlab and SPSS for feature extraction and analysis, but by using OpenCV it is possible to build more effective systems, with processing times that are suitable for use in real situations. Using OpenCV also simplifies the distribution of software due to permissive licensing, and it lowers the cost

of development, use and maintenance because there are no purchases or licensing fees. Finally, OpenCV is portable, meaning that any machine that is able to run C is also likely to be able to run OpenCV. Furthermore, OpenCV has been used on Windows, Linux, MacOS and Android systems.

The proposed system starts with the image acquisition process, where images are selected for further processing. These will undergo preprocessing in order to improve the image contrast in addition to other enhancements. The preprocessed images will then be used to extract a number of features, such as the area, the mean and the standard deviation of on pixels. Four nonlinear classifiers, namely a binary decision tree, a k-nearest neighbour classifier, and two support vector machines, using radial basis function and polynomial function kernels respectively, will then be trained on the training set to find an optimal way to group images into their respective classes. Finally, in the prediction phase, where the system might ultimately be used to assist the clinician, the images are classified into two main cases: normal or diabetic retinopathy. Figure 4.1 presents the block diagram of the proposed system for automating the screening and classification of diabetic retinopathy.

Figure 4.1 Block diagram of the proposed general automatic screening and classification of diabetic retinopathy

4.1.1 Image Preprocessing

Preprocessing is the process of image data improvement, involving the enhancement of some image characteristics or features for the next stage of processing. The image preprocessing techniques involved in the present work include Greyscale Conversion, Contrast Limited Adaptive Histogram Equalisation, Discrete Wavelet Transform, Filtering and Morphological Operations.

The first preprocessing technique used is the conversion of the colour fundus image into a greyscale image, as greyscale is usually a better format for image processing. A greyscale image has pixels of a single value, namely its intensity information. It is also known as a "black and white" image. The intensity is calculated by using a common formula combination of 30% of red, 59% of green and 11% of blue.

The Adaptive Histogram Equalisation (AHE) is a computer image processing technique for improving the image's contrast. The difference between the adaptive histogram equalisation and the ordinary histogram equalisation is that the adaptive histogram equalisation computes several histograms for different sections of the image, and subsequently distributes the lightness values. This technique is used to improve local contrast and enhance more details of the image. However, the adaptive histogram equalisation has its limitations, as it produces over-amplification of noise in the homogeneous regions of an image. Therefore, the Contrast Limited Adaptive Histogram Equalisation (CLAHE) is used in the proposed system in order to prevent the over amplification of noise. CLAHE functions by clipping the histogram at the predefined value before computing the cumulative distribution function. Histogram equalisation processed image is obtained by mapping each pixel with level r_k in the input image into a corresponding pixel with level s_k in the output image, as given below (Gonzalez and Woods, 2002):

$$s_k = T(r_k) = \sum_{j=0}^{k} p_r(r_j) \qquad \textbf{(4.1)}$$

$$= \sum_{j=0}^{k} \frac{n_j}{n} \qquad k = 0, 1, 2, \ldots, L-1$$

Discrete wavelet transform is a variant of wavelet transform for which the wavelets are discretely sampled. The discrete wavelet transform is an *O(N)* algorithm and it is also often referred to as the fast wavelet transform. The Haar wavelet is implemented in the proposed system development as it is a simple wavelet transform and it is currently used in many methods of discrete image transforms and processing. Discrete wavelet transforms can be used to reduce the image size without losing much of the resolution. The implementation of discrete wavelet transform is necessary to overcome the limitation of the software used, where a warning is generated when the image is too big to fit on the screen. Therefore resizing of the image is required. Since the fundus images are of a high resolution and of quite a large size, the use of the Haar wavelet is recommended. As a result of the implementation of the Haar Wavelet on the proposed system, the size of the fundus images are reduced by half, from 1500x1152 to 750x576.

Image filtering is used to improve the image quality or to restore a digital image which has been corrupted by some noise. A comparison of the performance between three different edge operators, i.e., Sobel, Prewitt and Kirsch has been proposed for the detection and segmentation of blood vessels in the colour retinal images (Karasulu, 2012). The experimental results show that the edge-based segmentation using the Kirsch compass templates is far superior to other methods. Moreover, the Kirsch operator can adjust the related threshold value automatically due to the image characteristics. Based on these reasons, the Kirsch operator has been chosen as an edge detection filter technique in the proposed system development. The Kirsch edge detection uses eight filters (i.e., eight masks for the related eight main directions) that are applied to a given image in order to detect edges. These eight filters are a rotation of a basic 3x3 compass convolution filter (i.e., single mask). The Kirsch filter is applied on

the wavelet transform image to create the eight filtered output images. The masks are distinct as given below (Karasulu, 2012):

$$M_0 = \begin{bmatrix} 5 & 5 & 5 \\ -3 & 0 & -3 \\ -3 & -3 & -3 \end{bmatrix}, M_1 = \begin{bmatrix} 5 & 5 & -3 \\ 5 & 0 & -3 \\ -3 & -3 & -3 \end{bmatrix}, M_2 = \begin{bmatrix} 5 & -3 & -3 \\ 5 & 0 & -3 \\ 5 & -3 & -3 \end{bmatrix}, \quad \textbf{(4.2)}$$

$$M_3 = \begin{bmatrix} -3 & -3 & -3 \\ 5 & 0 & -3 \\ 5 & 5 & -3 \end{bmatrix}, M_4 = \begin{bmatrix} -3 & -3 & -3 \\ -3 & 0 & -3 \\ 5 & 5 & 5 \end{bmatrix}, M_5 = \begin{bmatrix} -3 & -3 & -3 \\ -3 & 0 & 5 \\ -3 & 5 & 5 \end{bmatrix},$$

$$M_6 = \begin{bmatrix} -3 & -3 & 5 \\ -3 & 0 & 5 \\ -3 & -3 & 5 \end{bmatrix}, M_7 = \begin{bmatrix} -3 & 5 & 5 \\ -3 & 0 & 5 \\ -3 & -3 & -3 \end{bmatrix}$$

Morphological operations are used for certain purposes including image preprocessing, enhancing object structure, segmenting objects from the background and also for the quantitative description of objects (Sonka et al., 2008). In the proposed system development, morphology operators involving dilation and erosion are implemented to extract the blood vessels. A closing operation is defined as dilation followed by the erosion operator. Joshi and Karule (2012) implemented the closing operation for retinal blood vessel segmentation, where the disk shaped structuring element for the morphological operation is used. The dilation operates in greyscale images to enlarge brighter regions and it closes the small dark regions, while the erosion operator shrinks the dilated objects back to their original size and shape. As a result, the vessels being thin dark segments laid out on a brighter background, are closed by the closing operation. Figure 4.2 (a)-(f) shows the output after each of the preprocessing operations on a selected image.

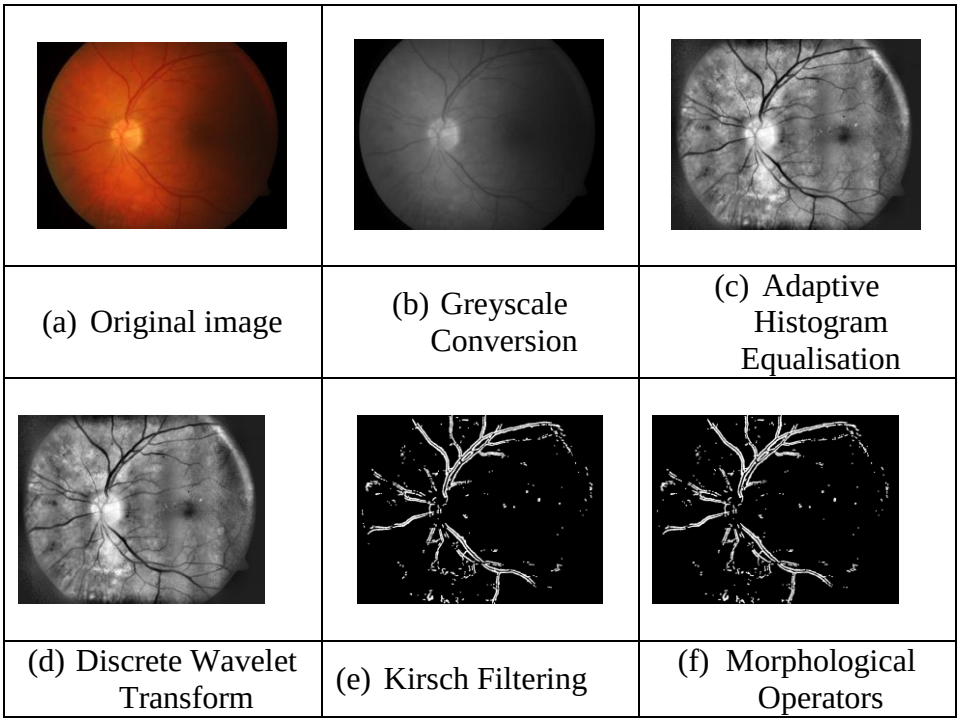


Figure 4.2 Image preprocessing

4.1.2 Feature Extraction

After performing the preprocessing techniques, feature extraction takes place in order to obtain the features from the given images. Features can be grouped into shape-based features, pixel-intensity-based features, Fourier-descriptor-based features and colour-based features. Within the preliminary system for the classification and screening of diabetic retinopathy, three basic shape features, including the area of on pixels and the mean and the standard deviation, are extracted for the purpose of diabetic retinopathy detection. The three values have been chosen as they are basic features and suitable for the pre-processed candidate image. These values for both normal and diabetic retinopathy images are used in order to create a model for training. Table 4.1 presents the details of the feature extracted including the generated code.

Table 4.1 Feature extraction in the proposed system

Feature	Description	Snippet Code

Area of on pixels	Number of grey level pixels on the black and white image, where white pixels on are all pixels above a threshold of 100 pixels	maxS = cvGet2D(gray, y, x);
		val = maxS.val[0];
		if(val > 100) {
		count++;
		sum += val; }

Mean	Mean value of on pixels	mean = sum / count;

Standard deviation	Standard deviation of on pixels	maxS = cvGet2D(gray, y, x);
		val = maxS.val[0];
		if(val > 100) {
		count++;
		val = (mean-val);
		sum += val*val; }
		sdv = sqrt(sum) / count;

4.1.3 Classification

The extracted feature values from the step described above have been passed to the classification stage. The PRTools, a Matlab toolbox for pattern recognition has been used to implement the classifiers (Duin et al., 2007). Nonlinear classifiers can provide better classification results compared to linear classifiers. Therefore, four nonlinear classifiers, namely the binary decision tree classifier, the k-nearest neighbour classifier, the radial basis function (RBF) kernel based support vector classifier and the polynomial kernel based support vector classifier have been selected to be trained on images and to group them into two classes, i.e., normal and diabetic retinopathy respectively, based on the three extracted features. The decision tree is a classifier in the form of a tree structure. It classifies instances by starting at the root of the tree and moving through it until a leaf node is reached. In the k-nearest neighbour classifier, the object is classified by a 'majority vote' of its neighbours, with the object being assigned to the most common class among its *k* nearest neighbours. The 1-nearest neighbour rule (1-NN) is used in the particular implementation of the system. A support vector machine (SVM) performs the classification by constructing an *N*-dimensional hyperplane that optimally separates the data into two categories. The support vector machine classifier can use various kernel functions, such as linear, polynomial or a radial basis function. The kernel function transforms the data into a higher dimensional space in order to be able to perform the separation in the nonlinear region. Two different

types of kernel functions provided in Matlab for SVM classification were used, i.e., the second order polynomial kernel SVM, *svc (ATrain, 'p', 2)*, and the radial basis function kernel SVM, *rbsvc (ATrain)*. The results show that the RBF kernel outperformed the results obtained by the second order polynomial kernel.

4.1.4 System Results and Evaluation

Figure 4.3 shows the user interface snapshot of the proposed developed system. The performance (misclassification error) of the four classifiers is presented in Table 4.2. Since the dataset is hugely unbalanced, the minority class was oversampled by duplication in order to balance it. The DIARETDB0 data is split randomly into 90% for training and the remaining 10% for testing. The process is repeated ten times in a cross-validation procedure in order to generate unbiased results. The average results on the ten runs for each of the four classifiers are then reported. The four machine learning classifiers were chosen to show the variance performance of different categories of algorithms in machine learning, i.e., clustering, classification and regression. For example, for the classification category, Support Vector Machines and k-nearest neighbour were used, and for the regression category, the binary decision tree was used. For more clarity, in Table 4.2, the confusion matrix for the first out of the ten experiments is presented, in order to show the relative performance of the four classifiers. A total of 130 colour fundus images, which consists of 110 normal images and 20 diabetic retinopathy images, were used initially. Later, the diabetic retinopathy images were duplicated to contribute the same number as the normal images. As a result, both normal and diabetic retinopathy classes constitute a total of 220 images, where each class has 110 images, respectively. A 10% from the 220 images, which total to 22 images, were used for the testing part, dividing 11 images for the normal class and another 11 images for the diabetic retinopathy class. The values of true positives, false negatives, false positives and true negatives can be extracted from the generated confusion matrix for the calculation of specificity, sensitivity and accuracy of the system. For example, for the binary decision tree, the value of true positives is 6, false negatives is 5, false positives is 0 and the true negatives is 11. The classification performance of the diagnosis system is assessed using the accuracy of the individual classifiers and also their specificity and sensitivity. The experimental results show that

the four classifiers, and especially the k-nearest neighbour, are well able to identify both classes, i.e., the normal and the diabetic retinopathy (DR) cases. All four classifiers had more success in identifying the diabetic retinopathy cases, as there were more examples of such images in the database. As a comparison, the system results proposed by Priya and Aruna (2011) showed a sensitivity of 99.45%, specificity of 100% and accuracy of 98.92% for the Support Vector Machine classifier. In addition, the experimental results in (Priya and Aruna, 2012) showed that the results were 98%, 96% and 97.6% for sensitivity, specificity and accuracy, respectively, for Support Vector Machine, while for Probabilistic Neural Network the results were 90% for sensitivity, 88% for specificity and 89.6% for accuracy.

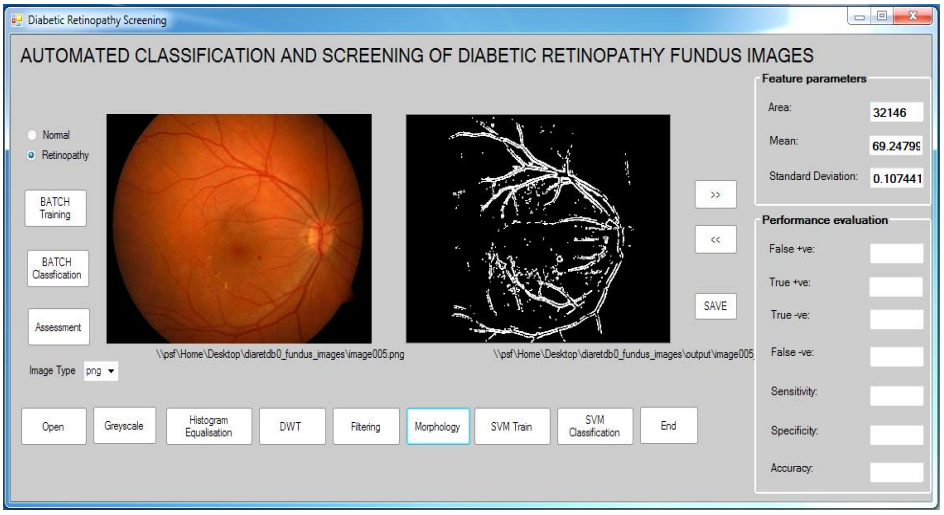


Figure 4.3 Snapshot of the proposed system user interface

Table 4.2 Average results when using the four classifiers

	Binary decision tree	k-nearest neighbour	RBF kernel SVM	Polynomial kernel SVM
Misclassification error	0.2091	0.01364	0.0909	0.3182
Accuracy	0.7909	0.9864	0.9091	0.6818
Specificity	1	1	1	0.5545
Sensitivity	0.5818	0.9727	0.8182	0.8091
Confusion matrix for the first experiment Labels (1 : Normal, 2: DR)	True Labels | Estimated Labels 1 2 | Totals 1 | 11 0 | 11 2 | 5 6 | 11 Totals | 16 6 | 22	True Labels | Estimated Labels 1 2 | Totals 1 | 11 0 | 11 2 | 0 11 | 11 Totals | 11 11 | 22	True Labels | Estimated Labels 1 2 | Totals 1 | 11 0 | 11 2 | 2 9 | 11 Totals | 13 9 | 22	True Labels | Estimated Labels 1 2 | Totals 1 | 6 5 | 11 2 | 2 9 | 11 Totals | 8 14 | 22

A general automatic system for screening and classification of diabetic retinopathy using fundus images has been developed. The classification area of the system can be enhanced by building an ensemble of classifiers. Unbalanced learning techniques can also be considered in order to train the individual classifiers in the ensemble. In addition, more sophisticated features will be used in the future work to properly discriminate between the various diabetic retinopathy signs (i.e., different features extraction for microaneurysms, haemorrhages, exudates, etc.). The system will also be extended to obtain more details of the diabetic retinopathy classification, namely to classify them into the following cases: no apparent retinopathy, mild non-proliferative, moderate non-proliferative, severe non-proliferative and proliferative DR. In addition to the classification diagnosis, the system can be improved to provide the recommended follow-up schedule for each stage, as underlined by the American Academy of Ophthalmology, in order to become a complete system to be used in a diabetic retinopathy screening practice.

4.2 Microaneurysms Detection

Microaneurysms, which are the earliest visible sign of diabetic retinopathy, appear as small dots on the retina. The early detection of microaneurysms is the first step in preventing diabetic retinopathy. Since the detection of microaneurysms is important and challenging, four variants of system development (System II – System V) which introduce different configurations and different techniques, are presented in this chapter (see also Rahim et al., 2015a, 2015b).

4.2.1 Automatic Detection of Microaneurysms in Colour Fundus Images Using Vessel Segmentation and Features Extraction (System II)

The system for the automatic detection of microaneurysms presented in this section consists of four main parts, namely, the image acquisition, the image preprocessing, the feature extraction, and the classification, using several machine learning techniques. System II is evaluated using the Standard Diabetic Retinopathy Database Calibration Level 1 (DIARETDB1), containing 89 colour fundus images (Kauppi et al., 2007).

There are 75 images with microaneurysms and the remaining 14 images were identified as showing no signs of microaneurysms.

The initial stage of the proposed system is the image acquisition process, followed by the preprocessing process. The preprocessed images are then used to extract a number of features. Four nonlinear classifiers, namely a binary decision tree, a k-nearest neighbour classifier, and two support vector machines, using radial basis function and polynomial function kernels respectively, are then trained on the training data to find an optimal way to group images into their respective classes. Finally, in the classification phase, the images are classified as to whether microaneurysms are present or not. The overall process of microaneurysm detection is shown in Figure 4.4.

Figure 4.4 Block diagram of the proposed automatic detection of microaneurysms

4.2.1.1 Image Preprocessing

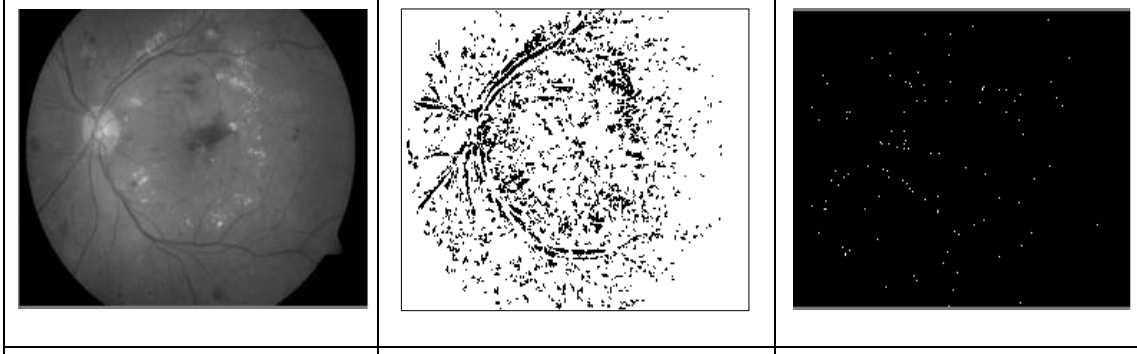
Preprocessing is used for image improvement. Greyscale Conversion and Shade Correction are the preprocessing techniques used in the proposed system.

Firstly, the colour fundus image is converted into the greyscale format for improved contrast. The second technique is shade correction, where the background image is estimated and later subtracted from the original image. The non-uniform illumination in the image needs to be corrected if the presence of microaneurysms in this area is to be correctly detected. The first step is to estimate the background using the morphological opening technique. The function *imopen* in Matlab (MathWorks, 2014) is used to perform a morphological opening of the greyscale image (with the structuring element of 12 pixels and disk shape). The second step is to subtract the background image from the original image (using the *imsubtract* function). The shade correction process is then continued, by increasing the image contrast (using the function *imadjust*), followed by thresholding of the image (by using *im2bw* function), and finally by the removal of the background noise (using *bwareaopen*). As a result, the thresholded image is inverted and the final output shows only the fundus image area.

After the greyscale conversion and shade correction, vessel segmentation is then performed. The vessels are extracted from the shade corrected image using a morphological operation. The image is closed using a disc shaped structuring element of 5 pixels. The shade corrected image is filled to eliminate holes in the vessels. Later, the filled image is subtracted from the closed image to give a vessel difference image. The image is thresholded to obtain binary images containing the vessels. The binary image is subtracted from the Gaussian filtered image, so that the final image has vessel free candidates.

In addition to the two main preprocessing methods of greyscale conversion and shade correction, other image preprocessing techniques can also be implemented, such as the green channel conversion, the median filter, the Gaussian filter and the Contrast Limited Adaptive Histogram Equalisation. In addition, four of the blood vessel extraction techniques can be implemented, including the Kirsch Template, the Frangi Filter, Local

Entropy and Entropic Thresholding. Figure 4.5 shows the output after the preprocessing operations are performed on a selected image.



(a) Greyscale Conversion	(b) Shade Correction	(c) Vessel Segmentation

Figure 4.5 Preprocessing the output image

4.2.1.2 Feature Extraction

After performing the preprocessing tasks, feature extraction takes place in order to obtain relevant features from the given images. Since a microaneurysm has specific features, such as a circular shape and a red colour, appropriate features should be extracted to ensure reliable feature extraction and classification. Sopharak and colleagues (2013) have listed some useful features for microaneurysm detection based on shape, pixel intensity, Fourier descriptor and colour. Features for the purposes of microaneurysm detection, such as the area of the pixels, the perimeter of the object, the major and minor axis length, its aspect ratio and its circularity have been chosen and extracted in the second system. These values are used to extract microaneurysms as they are appropriate for the characteristics of the microaneurysms. Table 4.3 presents the details of the features extracted in our system.

Table 4.3 Feature extraction in the proposed microaneurysms detection system

Feature	Description
Area of pixels in the candidate object	The actual number of pixels in the region
Perimeter of the object	The distance around the boundary of the region
Major Axis Length of the candidate object	The length (in pixels) of the major axis of the ellipse that has the same normalised second central moments as the region
Minor Axis Length of the candidate object	The length (in pixels) of the minor axis of the ellipse that has the same normalised second central moments as the region
Aspect ratio	Major Axis Length divided by the Minor Axis Length
Circularity	Roundness of the candidate, *((4*pi*Area) / (Perimeter. ^2))*

4.2.1.3 Classification

Classification was carried out using the PRTools package (Duin et al., 2007) in Matlab. In the second system, presented in this section, the classifiers selected and implemented for image classification purposes were: the binary decision tree classifier, the 1-nearest neighbour rule (1-NN) classifier, the radial basis function kernel based support vector classifier and the second order polynomial kernel based support vector classifier.

4.2.1.4 System Results and Evaluation

Figure 4.6 shows the user interface snapshot of the proposed developed system. The performance (misclassification error) of the four classifiers is presented in Table 4.4. Since the dataset is imbalanced, containing 75 images with signs of microaneurysms and only 14 normal images, the minority class was therefore oversampled by one-time duplication in order to avoid having an overly imbalanced dataset. The DIARETDB1 data is split randomly into 90% for training and the remaining 10% for testing. The process is repeated ten times in a cross-validation procedure in order to generate unbiased results. The average results on the ten runs for each of the four classifiers are then reported.

The accuracy, sensitivity and also the specificity of the individual classifiers are presented in Table 4.4 to measure classification performance. The accuracy of the four classifiers i.e., the binary decision tree and the 1-nearest neighbour is 0.9091, while the

radial basis function kernel and the second order polynomial kernel based support vector classifier is 0.7273. The experimental results show that the four classifiers are able to identify both classes, i.e., the "microaneurysms detected" and the "no microaneurysms" classes. The binary decision tree and the k-nearest neighbour classifiers yielded very good results.

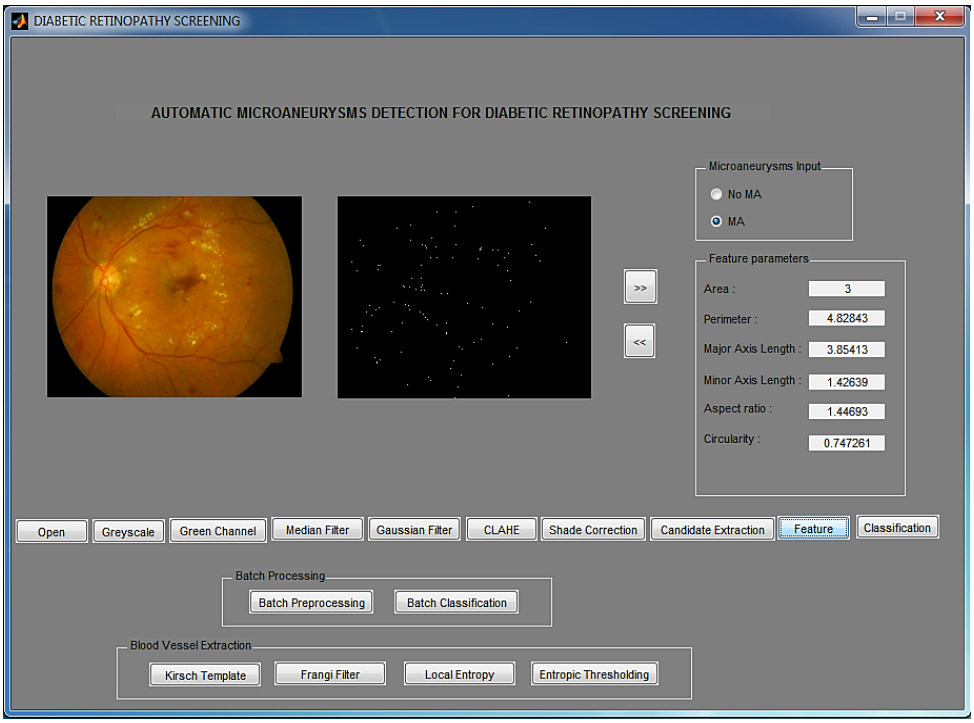


Figure 4.6 Snapshot of the proposed system user interface

Table 4.4 Average results when using the four classifiers

	Binary decision tree	k-nearest neighbour	RBF kernel SVM	Polynomial kernel SVM
Misclassification error	0.0909	0.0909	0.2727	0.2727
Accuracy	0.9091	0.9091	0.7273	0.7273
Specificity	1	1	0.3333	0
Sensitivity	0.875	0.875	0.875	1

4.2.2 Automatic Detection of Microaneurysms in Colour Fundus Images Using a Combination of Image Preprocessing Techniques and Circular Hough Transform (System III)

The third system proposed here is an automatic detection of microaneurysms, which introduces the combination of the preprocessing techniques and the Circular Hough Transform for the localisation and detection of microaneurysms in colour fundus images. For the third proposed systems, 40 fundus images of three different sizes (768 x 576, 1058 x 1061 and 1389 x 1383) have been used for evaluation from the Retinopathy Online Challenge (ROC) public database (Niemeijer et al., 2010).

The Circular Hough Transform technique has been previously proposed for the detection of microaneurysms in two types of photography modes, i.e., in retinal fluorescein angiographic images (Abdelazeem, 2002) and also in digital red-free photographs (Hipwell et al., 2000). The application of the Circular Hough Transform for the detection of microaneurysms in the colour mode (another type of fundus photography mode) was therefore explored. In the colour mode, the retina is illuminated by white light and examined in full colour. The red-free or monochromatic mode is where the imaging light is filtered to remove red colours, which helps to improve the contrast of vessels and other structures. In the angiography mode, vessels are brought into high contrast by the intravenous injection of a fluorescent dye, which produces a very high-contrast image of the vessels. The detection of microaneurysms in colour fundus images is more challenging compared to angiography and red-free types.

The initial stage of the proposed system is the image acquisition process, followed by the preprocessing process. Following this, the detection of the microaneurysm is performed using the Circular Hough Transform method. Finally, in order to test the accuracy of the microaneurysms detection system compared to the ROC annotation, statistical tests are performed for results analysis. The overall process of microaneurysm detection is presented in Figure 4.7.

Figure 4.7 Block diagram of the proposed automatic detection of microaneurysms using Circular Hough Transform

4.2.2.1 Image Preprocessing

A combination of preprocessing techniques, i.e., a Greyscale Conversion and Contrast Limited Adaptive Histogram Equalisation are used in the system development. The proposed preprocessing techniques are used to help increase the contrast of the colour fundus images. The uses of colour fundus images are more challenging compared to other modes of fundus photography examination: angiography and red-free. Appropriate techniques must therefore be implemented in order to improve the contrast of the fundus images for improved visualisation and detection.

4.2.2.2 Circular Hough Transform

The Circular Hough Transform (CHT) is implemented in the proposed system to locate microaneurysms, due to their circular shape. In addition, CHT is also useful in detecting the optic disc in a diabetic retinopathy screening system. The Hough Transform has been used for optic disc localisation by Noronha and other colleagues (2006).

Meanwhile, the same method was used to detect the early signs of diabetic retinopathy, represented by microaneurysms (Abdelazeem, 2002).

The Hough Transform can be used to detect lines, circles or other parametric curves. It can be used to determine a circle when a number of known points fall on the perimeter. The objective is to find the (*a*, *b*) coordinates of the centres at (*x*, *y*) on a circle of radius *R*. The Hough Transform offers some advantages, such as simplicity, ease of use, the effective handling of missing and occluded data and the fact that it can be adapted to many types of forms, other than lines. However, the limitations of the Hough Transform include the complex computation involved for objects with many parameters, the detection of one single type of object, difficulty in determining the length and position of a line segment and finally, that it cannot separate collinear line segments (Solberg, 2009).

Firstly, the radius of the microaneurysm in the fundus images is calculated (using the function *imdistline*). Based on the radius range specified, the system will find the circles in the fundus images using CHT (through the *imfindcircles* function). Finally, after finding the circles in the image based on the radius range, a circle is then created on the current axes (using the function *viscircles*). The output of the third proposed system in the localisation and detection of microaneurysms is shown in Figure 4.8.

Figure 4.8 Microaneurysms detection by using the Circular Hough Transform

4.2.2.3 System Results and Evaluation

Figure 4.9 shows the user interface snapshot of the proposed developed system. The performance analysis of the system and the expert annotation are presented in Table 4.5 and Table 4.6, respectively. The number of microaneurysms detected by the expert and the developed system are calculated and compared. The presence of any number of microaneurysms is represented as diabetic retinopathy (microaneurysms detected) and if there is no microaneurysm detected, it is considered as normal (microaneurysm not detected). Two types of statistical tests were performed to test the system performance compared to the expert diagnosis. The T-test is used to test the mean differences between the annotated images and the system output, and the results are presented in Table 4.5. The fundus images (forty in total) diagnosed by the expert and by the system were then compared with the T-test analysis. Firstly, a descriptive statistical analysis was conducted and the results, as shown in Table 4.5, indicate that there is only a small difference in the mean for the annotated images and that of the system (1.78 and 1.88, respectively). The inferential statistical analysis (i.e., T-test) result indicates a *p*-value of 0.253. This shows that the means of the annotated images and the system output are not significantly different.

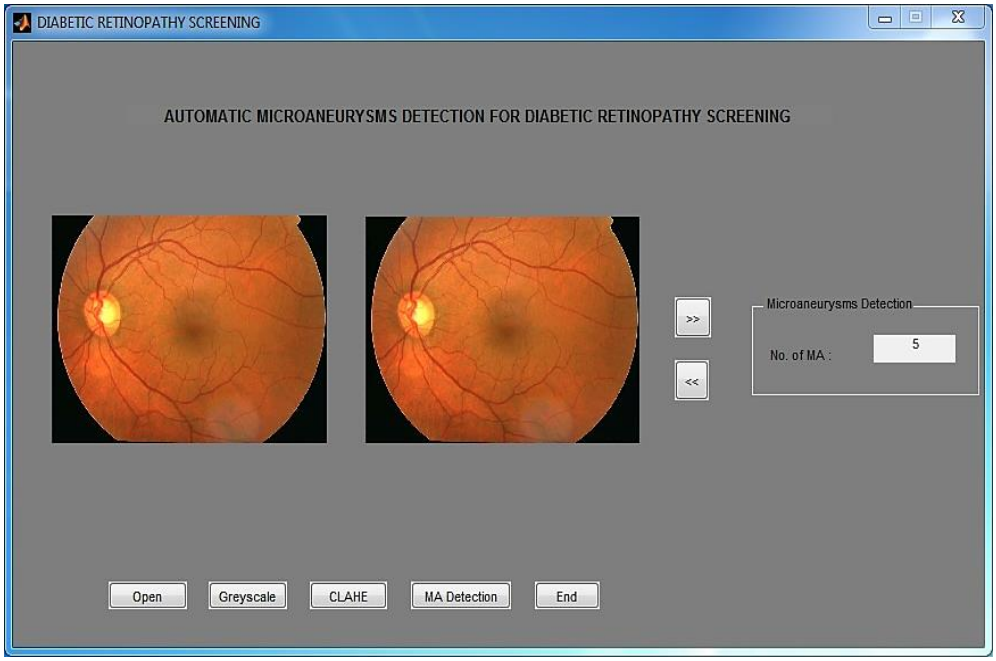


Figure 4.9 Snapshot of the user interface of System III

Table 4.5 T-test analysis

*n=40

		Mean	Standard Deviation	Standard Error Mean	*p*-value
Pair Tested					0.253
	Expert	1.78	0.423	0.067	
	System	1.88	0.335	0.053	

*n=Number of fundus images diagnosed by the expert and the system

The Chi-square test was also used to compare the two groups (i.e., the expert diagnosis and the system diagnosis). In addition, the Chi-square test was used to explore the relationship between these two categorical variables, as the results will help determine whether the system findings are more likely to be different from the expert findings, or in this case whether or not the expert is more likely to successfully identify diabetic retinopathy than is the system. The results generated by the Chi-square test are shown in Table 4.6, where the Chi-square test indicates a *p*-value of 0.239. Thus, it can be concluded that the system findings are more likely to be no different to the expert findings. In addition, Table 4.6 also shows the results of a cross tabulation generated to descriptively compare the methods of assessment between two groups: expert and system diagnosis for both normal and diabetic retinopathy categories. The results show the expert diagnosed 9 images as normal and 31 images as having diabetic retinopathy, while the developed system diagnosed 5 images as normal and the remaining 35 images as belonging to the diabetic retinopathy category, providing a further indication of the similarities between the two sets of diagnosis.

Table 4.6 Chi-square analysis

*n=80

	Classification			
	Normal n (%)	**DR n (%)**	**Total n**	**Chi-Square Test Statistic**
Method of Assessment				χ^2 (1, n=80) = 1.385, *p*=0.239
Expert	9 (22.5)	31 (77.5)	40	
System	5 (12.5)	35 (87.5)	40	

*n=Number of fundus images diagnosed by the expert and the system

4.2.3 Automatic Detection of Microaneurysms in Colour Fundus Images Using Fuzzy Image Processing (System IV)

The fourth system applies a fuzzy technique for image preprocessing in the detection of microaneurysms. As explained in Section 4.2.2.1 above for the third system, the colour fundus images are more challenging compared to the other modes of fundus photography examination. Therefore, in order to obtain better visualisation and accurate detection, contrast enhancement should be implemented.

The fourth system proposes the implementation of a fuzzy preprocessing technique, the Fuzzy Histogram Equalisation. The fuzzy preprocessing techniques were used for contrast enhancement in the medical digital images, such as pathology images (Garud et al., 2011) and also other non-medical images (Sheet et al., 2010). The performance of the fuzzy preprocessing techniques reported in previous work is promising. Therefore, the suitability of the fuzzy preprocessing technique for the screening of diabetic retinopathy using colour fundus images will be investigated and proposed.

Contrast enhancement produces a better image than the original by changing the pixel intensities (Sheet et al., 2010). There are several contrast enhancement techniques available: Histogram Equalisation (HE), Contrast Limited Adaptive Histogram Equalisation (CLAHE), Histogram Stretching and brightness preserving histogram modification approaches. Histogram equalisation is a technique for adjusting image intensities in order to enhance contrast, in which the grey-level values are uniformly distributed. Adaptive histogram equalisation is a more advanced version of histogram equalisation which divides the image into smaller tiles, applies the histogram equalisation to each tile, and then interpolates the results. This adaptive histogram equalisation includes limits on how far the contrast should be changed, namely the Contrast-Limited Adaptive Histogram Equalisation, CLAHE.

Sheet et al. (2010) proposed a modified technique of the brightness preserving equalisation called the Brightness Preserving Dynamic Fuzzy Histogram Equalisation (BPDFHE). This technique is explained at length in Section 2.7. The representation and processing of images in the fuzzy domain allows the technique to handle the inexactness of grey level values in a better way in order to improve the overall performance. The

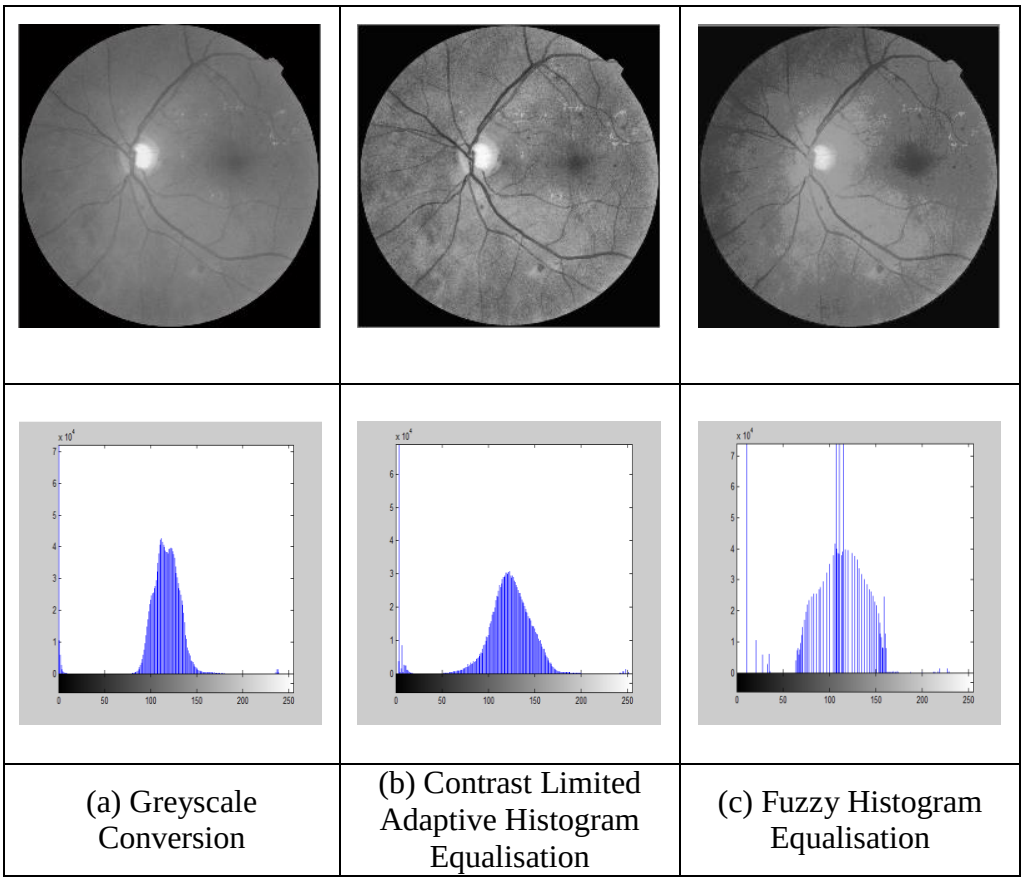
technique proposed by Sheet et al. (2010) is used for contrast enhancements in digital pathology images (Garud et al., 2011). The performance of this technique has been compared with HE and CLAHE and, as a result, the BPDFHE preserved the image brightness better than the other two techniques. Good performance of the BPDFHE technique especially in medical images such as pathology images is reported by Garud et al. (2011). This technique has been explored as a preprocessing technique for the proposed detection of microaneurysms in diabetic retinopathy screening.

The first stage of the proposed system is the image acquisition process, the second is preprocessing process, the third is the detection of microaneurysms using the Circular Hough Transform method and, finally, in order to test the accuracy of the microaneurysms detection system with the ROC annotation, the statistical tests are used for analysis. System IV(a) is similar to the third system presented in Section 4.2.2, which implemented the Greyscale Conversion, Contrast Limited Adaptive Histogram Equalisation and Circular Hough Transform. The difference between these systems is that the third system bases its categorisation of Normal (no microaneurysms detected) or Diabetic Retinopathy (microaneurysms detected) on the presence of microaneurysms. System IV on the other hand, categories results into microaneurysms detected or undetected based on the number of microaneurysms detected between the expert and the developed system. The overall process of microaneurysms detection is presented in Figure 4.10.

4.2.3.1 Image Preprocessing

A combination of preprocessing techniques including a Greyscale Conversion and a Contrast Limited Adaptive Histogram Equalisation (CLAHE) are implemented for the first system, System IV(a), while for the second system, System IV(b), a combination of both a Greyscale Conversion and a Fuzzy Histogram Equalisation is proposed. Figure 4.11 shows both the output and the histogram for the intensity of the fundus image after the preprocessing techniques have been applied, i.e., Greyscale Conversion, CLAHE and Fuzzy Histogram Equalisation.

Figure 4.10 Block diagram of System IV for the automatic detection of microaneurysms



(a) Greyscale Conversion	(b) Contrast Limited Adaptive Histogram Equalisation	(c) Fuzzy Histogram Equalisation

Figure 4.11 Preprocessing the output image

4.2.3.2 Microaneurysms Detection

The Circular Hough Transform technique is implemented in the fourth system to detect the microaneurysms, as this technique has a good ability to detect circular shapes. The background on the Circular Hough Transform technique is presented in Section 4.2.2.2.

4.2.3.3 System Results

Figure 4.12 shows the user interface snapshot of the proposed developed system. Generally, the interfaces for both systems are similar, but the implementation of the preprocessing techniques is different, as mentioned in Section 4.2.3.1 above.

The statistical result comparisons for both systems are presented in Table 4.7. The T-test and the ANOVA test were performed to test the mean differences between the annotated images and the system results based on the number of microaneurysms detected by the expert and by the system. The first system, using a combination of Greyscale Conversion and Contrast Limited Adaptive Histogram Equalisation, shows that the means of the annotated images (7.48) and the system output (18.98) are significantly different. On the other hand, the second system, which implemented the Greyscale Conversion and the Fuzzy Histogram Equalisation, shows that the means of the annotated images (7.48) and the system (9.33) are not significantly different. The inferential statistical analysis (i.e., T-test) result indicates a *p*-value of 0.006 and 0.484 for the first and the second system, respectively. Meanwhile, the results generated by the ANOVA test are also shown in Table 4.7, where the ANOVA test indicates a *p*-value of 0.380 for the first system and 0.961 for the second system. In addition, the first system (System IVa) produces the sensitivity of 0.8710, the specificity of 0.1111 and the accuracy of 0.7000. The second system (System IVb) which implemented the Fuzzy Histogram Equalisation generates better results where the sensitivity is 0.8387, the specificity increased to 0.5556 and the accuracy is 0.7750. Based on the results presented, it can be concluded that the implementation of the fuzzy preprocessing techniques provides better contrast enhancement for fundus images, hence, it greatly assists in the detection of microaneurysms, providing a more efficient and reliable performance of the diagnosis system.

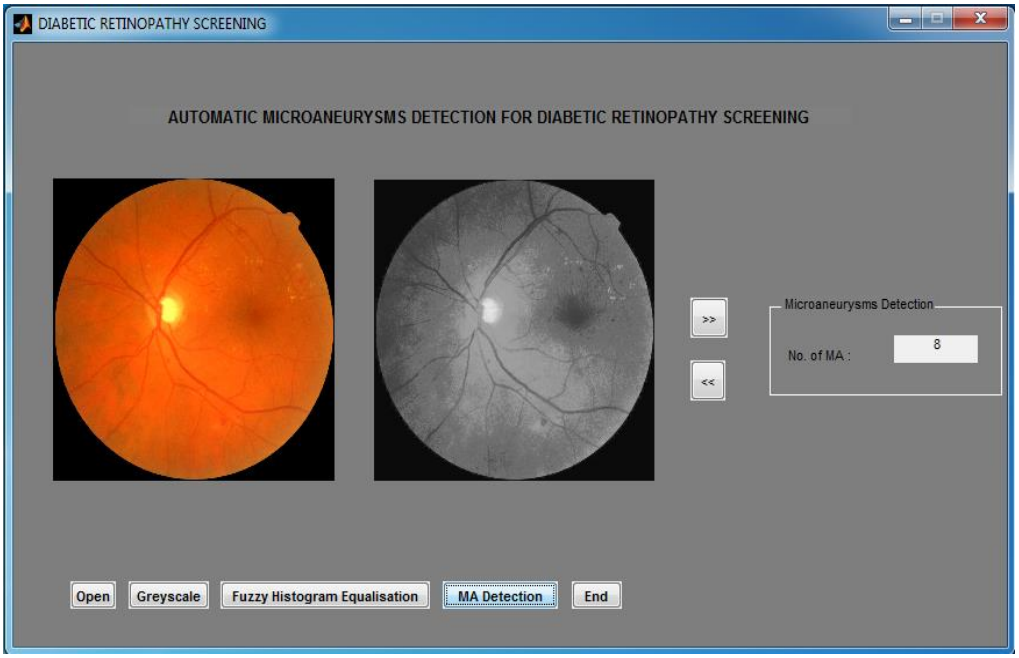


Figure 4.12 Snapshot of the user interface of System IV

Table 4.7 Summary results for Systems IV(a) and IV(b)

Features	System IV(a)	System IV(b)
Techniques	Greyscale Conversion, Contrast Limited Adaptive Histogram Equalisation, Circular Hough Transform	Greyscale Conversion, Fuzzy Histogram Equalisation, Circular Hough Transform
Number of fundus images diagnosed	40	40
Confidence Interval	95%	95%
T-test *p*-value	0.006	0.484
T-test mean:		
Expert	7.48	7.48
System	18.98	9.33
T-test standard deviation:		
Expert	10.268	10.268
System	21.021	11.425
T-test standard error mean:		
Expert	1.624	1.624
System	3.324	1.806
ANOVA test *p*-value	0.380	0.961

4.2.4 Automatic Detection of Microaneurysms Using Fuzzy Histogram Equalisation, Fuzzy Filtering and Fuzzy Edge Detection (System V)

Fuzzy image processing is a collection of different fuzzy approaches to the processing of the images. Fuzzy edge detection, fuzzy histogram equalisation and fuzzy filtering are among the fuzzy processing techniques that can be performed on images. In addition to the fuzzy histogram equalisation, which was presented in Section 4.2.3, the fuzzy filters for image filtering have been proposed by Patil and Chaudhari (2012), Toh (2010) and also Kwan (2003). In addition to using fuzzy histogram equalisation and fuzzy filters, fuzzy edge detection can also be performed.

In this section, in order to develop the proposed system, 600 fundus images from a novel data set, collected from the Melaka Hospital, Malaysia (which is presented in Section 3.9), have been used for evaluation. The system starts with the image acquisition process, where the system selects images for further processing. The selected images undergo preprocessing in order to improve image contrast in addition to other enhancements. The preprocessed images are then used to locate and detect the retinopathy signs, i.e., the microaneurysms. The numbers of microaneurysms detected are displayed. Finally, in the classification phase, the images are classified into two main cases: microaneurysms detected or microaneurysms not detected, based on the number of microaneurysms detected. The overall process of microaneurysm detection is presented in Figure 4.13.

Figure 4.13 Block diagram of System V for the automatic detection of microaneurysms

4.2.4.1 Image Preprocessing

The image preprocessing techniques involved in this present work include Greyscale Conversion, Adaptive Histogram Equalisation, Fuzzy Histogram Equalisation, Fuzzy Filtering and Fuzzy Edge Detection.

The first preprocessing technique used is the conversion of the colour fundus image into a greyscale image, as greyscale is usually the best format for image processing. Histogram equalisation is a computer image processing technique for improving the image's contrast. The proposed preprocessing techniques are used to help increase the contrast of the colour fundus images. As mentioned in Section 4.2.3.1, for System IV, the use of colour fundus images is more challenging compared to angiography and red-free which are the other modes of fundus photography examination. Therefore, appropriate techniques need to be implemented in order to improve the contrast of the fundus images for better visualisation and detection. The Brightness Preserving Dynamic Fuzzy Histogram Equalisation (BPDFHE) technique proposed by Sheet et al.

(2010), has been chosen as a preprocessing technique for the proposed detection of microaneurysms in diabetic retinopathy screening. This is due to its good performance and proven ability to work well for medical images, such as the pathology images presented by Garud et al. (2011).

Image filtering is used to improve the image quality or to restore a digital image which has been corrupted by some noise. The proposed system implemented the median filter by employing the fuzzy techniques. The Noise Adaptive Fuzzy Switching Median (NAFSM) filter is an extension to the Fuzzy Switching Median (FSM) filter developed by Toh and colleagues (2010). It worked well both in removing salt-and-pepper noise and preserving image details and textures, by incorporating fuzzy reasoning in correcting the detected noisy pixel. The technique is composed of two modules, which are the salt-and-pepper noise detection and the fuzzy noise cancellation module. This technique is explained in Section 2.7, together with the fuzzy histogram equalisation and fuzzy edge detection.

As outlined in Section 2.7, an edge is a boundary between two uniform regions. The edge can be detected by comparing the intensity of the neighbouring pixels. However, since uniform regions are not crisply defined, small differences of intensity between two neighbouring pixels do not always represent an edge, it might instead represent a shading effect. Therefore, the use of membership functions would overcome the problems by defining the degree of pixel as to whether it belongs to an edge or to a uniform region. The image gradients are created as the inputs of a Fuzzy Inference System (FIS) for edge detection. For each input, a zero-mean Gaussian membership function is specified, where if the gradient value for a pixel is 0 (region), then it belongs to the zero membership function with a degree of 1. Another membership function is added, which specifies the standard deviation from the zero membership function for the gradient inputs. As an output of the FIS, which is the intensity of the edge-detected image, the triangular membership functions (white and black) are specified. The values of the standard deviation and also the values of the triangular membership functions for the output can be changed in order to adjust the edge detector performance. Next, the FIS rules can be specified to make a pixel white if it belongs to a uniform region,

otherwise the pixel presents as black. Figure 4.14 shows the membership functions of the inputs and outputs for the edge detection purpose. For both inputs, which are the gradient of every pixel on both axes, the parameters for the Gaussian membership function consists of the central value or mean (0) and the standard deviation (0.1). Meanwhile, for the outputs of the edge detection, which are the intensities of the edge-detected image, there are three parameters required for the triangular membership function. The parameters are the start, peak and end of the triangles of the membership functions. The triplet parameter values for both white and black are (0.7, 0.9, 1) and (0, 1, 1), respectively. The fuzzy membership functions parameters were obtained by changing the parameter values until better performance of the edge detector and increased intensity of detected edges were produced. These parameters influence the intensity of the detected edges. The Gaussian fuzzy membership function was used due to the smoothness decision obtained, while the triangular function was chosen due to simplicity and computational efficiency. The implementation of both fuzzy membership functions for the edge detection provides better edge detection and more quality output image. Figure 4.15 shows the output after each of the fuzzy pre-processing operations on a selected image, as explained previously.

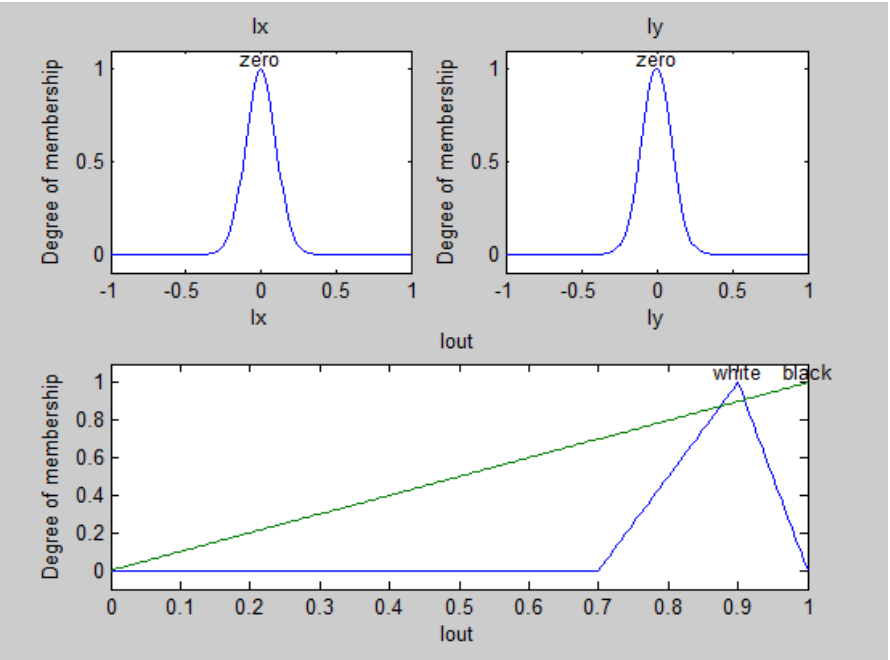


Figure 4.14 Membership functions for inputs and outputs

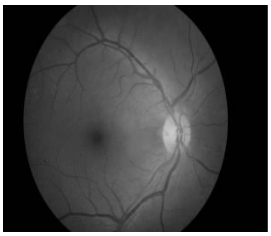
		
(a) Fuzzy Histogram Equalisation	(b) Fuzzy Filtering	(c) Fuzzy Edge Detection

Figure 4.15 Preprocessing the output image with fuzzy approaches

4.2.4.2 Localisation and Detection of Microaneurysms

After performing the preprocessing techniques, both localisation and microaneurysm detection takes place. In order to detect the circular microaneurysms satisfactorily, the Circular Hough Transform (CHT) technique is implemented in the proposed system. The implementation of the Circular Hough Transform uses the *imdistline* function in Matlab to calculate the radius of microaneurysms in the fundus images. The *viscircles* function that draws circles in the fundus image with a specified centre and radius onto the current axes is presented in Section 4.2.2.2.

4.2.4.3 Classification

The counting of microaneurysm will then takes place. The presence of any number of microaneurysms is represented as Diabetic Retinopathy, DR (microaneurysms detected), and if there is no microaneurysm detected, it is considered as normal or no retinopathy (microaneurysms not detected). The categorical types of the output whether Normal/No DR or DR will be used later for the analysis of the system performance. The categorical types from the expert diagnosis and the system generated are then compared. The nominal inputs from both expert and system are represented as 1 for Normal/No DR and 2 for DR. The average from the three experts will be used for the overall expert diagnosis. Later, the comparison between the overall expert diagnosis and the proposed system diagnosis will be completed and a statistical analysis of both performances will then be produced.

4.2.4.4 System Results and Evaluation

Figure 4.16 shows the user interface snapshot of the proposed developed system. The performance analysis summary of the proposed system, which utilises different techniques, is presented in Table 4.8. System V(a) implemented the greyscale conversion, histogram equalisation and Circular Hough Transform (CHT), while System V(b) proposed the implementation of the Fuzzy Histogram Equalisation in addition to the greyscale conversion and CHT. System V(c) and System V(d) proposed the implementation of other fuzzy image processing techniques, such as Fuzzy Filtering and Fuzzy Edge Detection respectively. Two types of statistical tests were performed to test the system performance compared to the expert diagnosis. Six hundreds fundus images diagnosed by the expert and the systems are involved in both tests. The results generated prove that, within the 95% confidence interval, the means of the annotated images (1.54) and the system with the fuzzy techniques such as Fuzzy Histogram Equalisation (1.49) and Fuzzy Edge Detection output (1.59) are not significantly different. Thus, it can be concluded that the system findings are more likely to be no different to the expert findings. However, the annotated images and the system with the fuzzy median filter (with mean 1.43) are significantly different and show the opposite. The inferential statistical analysis (i.e., T-test) result indicates a *p*-value of 0.00 (System V(a)), 0.92 (System V(b)), 0.00 (System V(c)) and 0.73 (System V(d)), respectively. The Chi-square test indicates a *p*-value of 0.00, 0.94, 0.00 and 0.81 for the four systems. In addition, Table 4.8 shows that the results generated compare descriptively to the methods of assessment between two groups: the expert and the system diagnosis for both normal and diabetic retinopathy cases. The analysis based on the presented results concludes therefore, that the implementation of the fuzzy preprocessing technique provides better contrast enhancement and other improvements for fundus images, hence, it greatly assists in detecting microaneurysms more efficiently therefore a reliable performance of the diagnosis system can be produced.

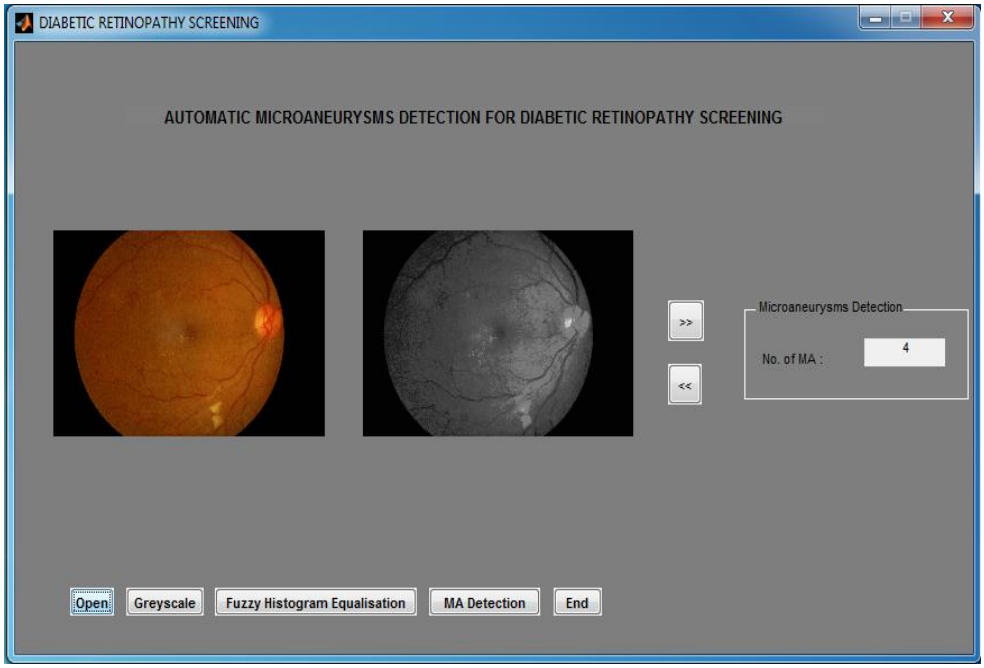


Figure 4.16 Snapshot of the proposed system user interface

Table 4.8 Summary results for System V(a), V(b), V(c) and V(d)

	System V(a)	System V(b)	System V(c)	System V(d)
Techniques	Greyscale, Histogram Equalisation, CHT	Greyscale, Fuzzy Histogram Equalisation, CHT	Greyscale, Fuzzy Median Filter, CHT	Greyscale, Fuzzy Edge Detection, CHT
T-Test Mean:				
Expert	1.54	1.54	1.54	1.54
System	1.67	1.49	1.43	1.59
T-Test *p*-value	0.00	0.92	0.00	0.73
Chi-Square *p*-value	0.00	0.94	0.00	0.81
Expert Count:				
No DR	276	276	276	276
DR	324	324	324	324
System Count:				
No DR	201	305	343	246
DR	399	295	257	354

4.3 Maculopathy and Diabetic Retinopathy Detection

Maculopathy is represented by yellow lesions near the macula and is a disease of the macula region of the retina. The macula is the centre of the retina and provides our central vision. The macula region is a very sensitive area in the centre of which is the fovea, a tiny area which is responsible for both detailed and colour vision (Taylor and Batey, 2012). The detection of maculopathy therefore is very important because the loss of vision at the fovea alone causes blindness. Maculopathy is present when there are any exudates, haemorrhages or microaneurysms in the macula region. However, the visible signs of maculopathy are only indirect markers for the possible presence of macula oedema, which is the swelling of the retina (Taylor and Batey, 2012). The presence or absence of the maculopathy will determine the need for treatment or referral. The referral to the ophthalmologist is assigned if maculopathy is present. If maculopathy is absent referral is not required and the screening will be repeated in one year's time. The combined detection of diabetic retinopathy and maculopathy therefore is vital in order to effectively assist the management of diabetic retinopathy screening.

In order to identify maculopathy, the localisation and the detection of both macula and fovea are essential, as maculopathy is represented by lesions in the macula region and the fovea is at the centre of the macula. Kumar et al. (2013) proposed an approach in detecting the macula by using bit plane decomposition and mathematical morphology methods. Mubbashar et al. (2011) presented an automated system for the localisation and detection of the macula in digital retinal images. The centring of the optic disc and the blood vessel extraction are performed prior to the detection of the macula. This is achieved by using the centre of the optic disc and by thresholding, followed by vessel enhancement and then locating the macula as the darkest pixels in the region. In addition, the detection of the macula is proposed by Akram et al. (2014) along with the detection of exudates. The system proposed a contrast enhancement, thresholding and blood vessel segmentation to detect the dark candidate, followed by the classification of some of the set features for macula detection through the use of a Gaussian Mixtures Model-based classifier. The localisation of the optic disc and the fovea in retinal fundus images is also proposed by Sekhar et al. (2008). Morphological operations and the Hough transform are implemented to locate the optic disc, while the fovea is located via

the spatial relationship with the optic disc and also from the spatial distribution of the macula. They defined the region of interest as an area in a sector that originates at the optic disc centre at an angle of 30° above and below the line between the optic disc centre and the centre of the retinal image disc.

Meanwhile, Punnolil (2013) proposed an approach for the grading of diabetic maculopathy through implementing the detection of retinal structures, such as the optic disc, the macula and the fovea followed by the detection of lesions including the exudates, haemorrhages and microaneurysms. These were later graded into classes of diabetic maculopathy using a multiclass Support Vector Machines (SVM) classifier based on the extracted features. Tariq et al. (2013) present a similar diabetic maculopathy grading system starting with the optic disc localisation and the vascular structure to extract the macula. Next, features such as area, compactness, mean intensity, mean hue and others are extracted from the exudates detection and used to classify different stages of maculopathy using a Gaussian Mixture Model-based classifier. The detection of diabetic maculopathy in retinal images is also investigated by Vimala and Kajamohideen (2014) through the use of morphological operations. The detection of macula is generated from the image preprocessing techniques such as green component extraction, filtering and adaptive histogram equalisation. Morphological operations are then performed, such as top-hat transform and bottom-hat transform. Other automatic gradings of diabetic maculopathy systems are proposed by Siddalingaswamy and Prabu (2010), Hunter et al. (2011) and Chowriappa et al. (2013). Siddalingaswamy and Prabu (2010) proposed the detection of the optic disc, fovea and macula region, based on the location and diameter of the optic disc, followed by the detection of the hard exudates using both clustering and mathematical morphological techniques. The classification into severity levels of maculopathy, which consist of mild, moderate and severe levels, is performed based on the location of exudates in the marked macular region. An automated diagnosis of the maculopathy system is presented by Hunter et al. (2011). Firstly, the optic nerve head and the fovea are detected in order to locate the macula region. Candidate lesions are then segmented, followed by feature extraction and, finally, classification by a multilayer perceptron. An ensemble selection for the feature-based classification of diabetic maculopathy images

is suggested by Chowriappa et al. (2013). This is based on extracting textural features and then using classifiers such as the hidden Naïve Bayes, Naïve Bayes, sequential minimal optimisation (SMO) and the tree-based J48 algorithm to classify the features into disease severity classes.

The detection of maculopathy is vital as it will eventually cause loss of vision if the affected macula is untreated. Therefore, some researchers are focusing on this challenging area and suggest several solutions for the detection of maculopathy on retinal images. However, fuzzy processing has not been implemented during the preprocessing stage within these previously reported maculopathy detection systems. Therefore, the proposed system implements a combination of fuzzy techniques for the image processing area of diabetic retinopathy and maculopathy detection. Two systems have been proposed for detecting diabetic retinopathy alongside maculopathy in this research work. The development of the first system (System VI) is explained in detail in Rahim et al. (2015c), while the second system (System VII) is presented in Rahim et al. (2016). Both systems have been evaluated with the 600 fundus images from the novel data set, collected from the Melaka Hospital, Malaysia, which is presented in Section 3.9.

4.3.1 Detection of Diabetic Retinopathy and Maculopathy in Eye Fundus Images Using Fuzzy Image Processing (System VI)

System VI implements a combination of fuzzy techniques in image preprocessing, which involves fuzzy filtering, followed by fuzzy histogram equalisation and finally fuzzy edge detection. System VI is different from System V presented in Section 4.2.4, as System V proposed individual system variants implementing different fuzzy processing techniques for the detection of microaneurysms. On the other hand, System VI proposed a novel detection system for diabetic retinopathy and maculopathy by combining several consecutive fuzzy image preprocessing techniques in one system, based on previous encouraging results for the use of fuzzy image processing obtained by System V. In addition, System VI is following the current practice observed by the ophthalmologist in the classification and grading of diabetic retinopathy and maculopathy, which classifies images into ten main classes, as explained in Section 3.9.

The system begins with the image acquisition process, where the system selects images for further processing. The selected images undergo preprocessing in order to improve the image contrast as well as perform other enhancements, with a combination of several fuzzy techniques. The preprocessed images are then used for feature extraction, where three features, namely, the area, the mean and the standard deviation of on pixels are extracted. Finally, in the classification phase, some machine learning classifiers are trained using these features to classify the images into their respective classes. Figure 4.17 presents the block diagram of the proposed system for the automatic screening and classification of diabetic retinopathy and maculopathy using fuzzy image processing techniques.

Figure 4.17 Block diagram of System VI for the automatic detection of diabetic retinopathy and maculopathy using fuzzy image processing

4.3.1.1 Image Preprocessing

Image preprocessing is the operation of improving the image data quality. Fuzzy approaches are implemented in this proposed version of the system at the preprocessing stage. The image preprocessing techniques involved in the present work include Greyscale Conversion, Fuzzy Filtering, Fuzzy Histogram Equalisation and Fuzzy Edge Detection. Similar proposed image preprocessing techniques, as in System V, are implemented due to their good performance. In order to calculate the white pixels from the edge-detected image, the output image is converted or inversed to produce the black and white image. Figure 4.18 shows the membership functions of the inputs and outputs for the edge detection purpose. For both inputs, which are the gradient of every pixel on both axes, the parameters for the Gaussian membership function consists of the central value or mean (0) and the standard deviation (0.1). Meanwhile, for the outputs of the edge detection, which are the intensities of the edge-detected image, there are three parameters required for the triangular membership function. The parameters are the start, peak and end of the triangles of the membership functions. The triplet parameter values for both white and black are (0, 1, 1) and (0, 0.7, 1), respectively. Figure 4.19 shows the output after each of the fuzzy pre-processing operations on a selected image.

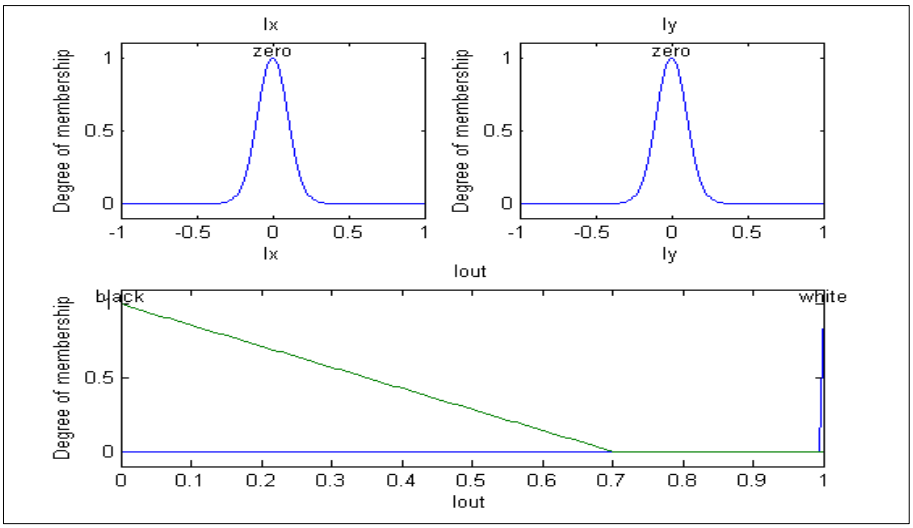


Figure 4.18 Membership functions for inputs and outputs

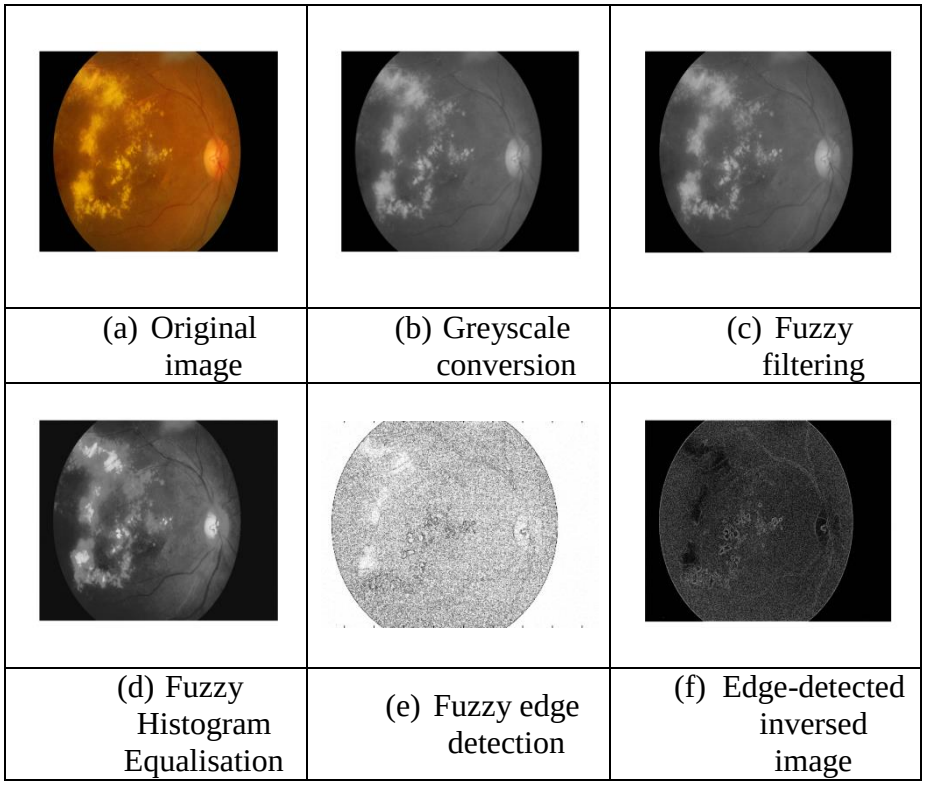


Figure 4.19 Preprocessing of the output image

4.3.1.2 Feature Extraction

After performing the preprocessing techniques, feature extraction takes place to obtain the features from the preprocessed images. Three preliminary features are proposed, namely, the area of on pixels and the mean and standard deviation which will be extracted for the purposes of detection. The first feature is the number of white pixels on the black and white image, while the second and third features are the mean value and the standard deviation of on pixels, respectively. These three shape-based features are suitable to be extracted from the edge-detected inversed output image. For example, the area of on pixels represents the detected maculopathy, which is the purpose of this developed system. Other more sophisticated features could be extracted in addition to these three proposed features in order to improve the classification performance.

4.3.1.3 Classification

The extracted feature values were used in the classification stage, where the PRTools Matlab toolbox (Duin et al., 2007) for pattern recognition was employed for this task. In order to generate a variety of results and a good performance analysis of the system, two types of classification were considered. First, the images have been classified into two classes, i.e., normal (276 images) and diabetic retinopathy (324 images). In addition, with the use of several machine learning classifiers, the images are then classified into ten classes, which provide more details, i.e., No Diabetic Retinopathy (DR) with 276 images, and the other nine detailed classes of the DR cases, which are: Mild DR without maculopathy (72 images), Mild DR with maculopathy (27 images), Moderate DR without maculopathy (85 images), Moderate DR with maculopathy (83 images), Severe DR without maculopathy (23 images), Severe DR with maculopathy (11 images), Proliferative DR without maculopathy (6 images), Proliferative DR with maculopathy (10 images) and Advanced Diabetic Eye Disease (ADED, with only 7 images). Several machine learning classifiers, such as the binary decision tree classifier and the 1-nearest neighbour classifier have been selected to train and classify images into these categories.

4.3.1.4 System Results and Evaluation

Figure 4.20 shows the user interface snapshot of the proposed developed system. The performance of the proposed system, including the misclassification error, accuracy of the individual classifiers and also the specificity and sensitivity of the two classifiers for both categories are presented in Table 4.9, based on the confusion matrix generated. Since the dataset is hugely imbalanced for some classes including mild DR with maculopathy, severe DR with and without maculopathy, proliferative DR with and without maculopathy and Advanced Diabetic Eye Disease (ADED), the minority classes were oversampled. This was achieved by running the system with images from these classes replicated several times in order to obtain various extracted feature values and balance the dataset. The developed dataset is split randomly into 90% for training and the remaining 10% for testing. The process is repeated ten times in a cross-validation procedure in order to generate unbiased results. The average results on the ten runs for each of the two classifiers are reported. The experimental results show that the two

classifiers, and especially the k-nearest neighbour, are able to identify well for both main categories. The two classifiers identified the diabetic retinopathy cases much better however in the two classes' case, as there were more examples of such images in the database compared to other example of the ten classes. The maculopathy can be seen clearly from the inversed edge-detected image and the area of on pixels will have a higher value for those images with maculopathy.

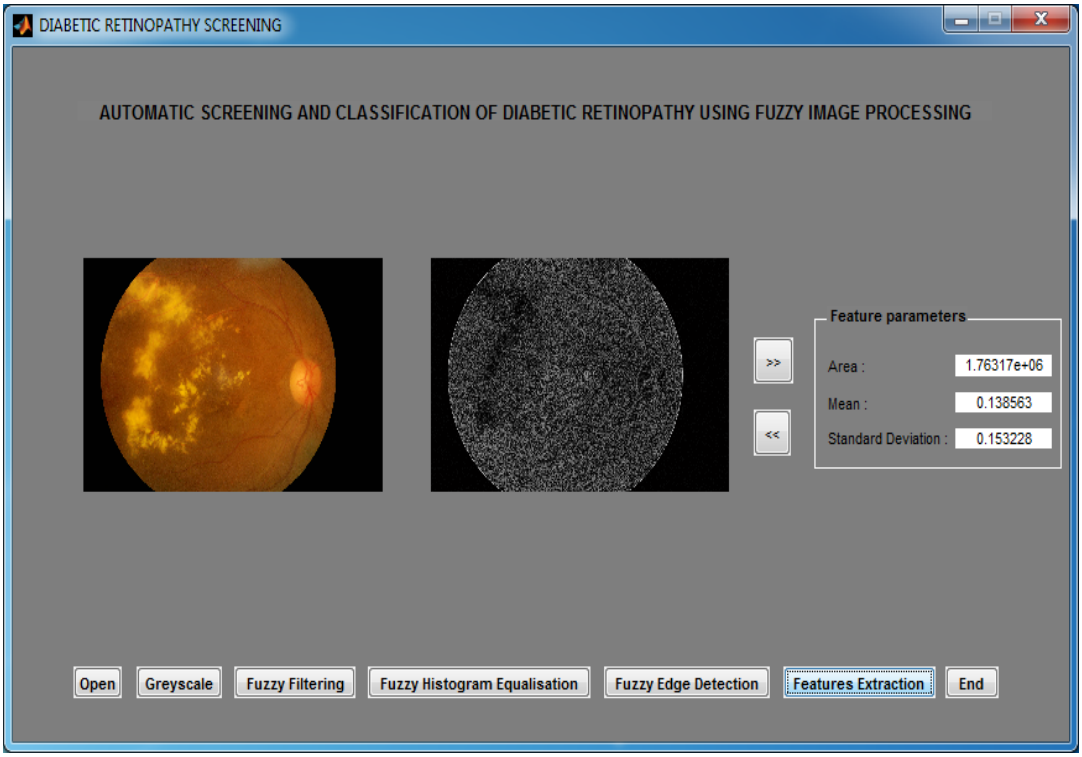


Figure 4.20 Snapshot of the proposed system user interface

Table 4.9 Summary results for System VI

	Category I : 2 classes		Category II : 10 classes	
	Binary decision tree	k-nearest neighbour	Binary decision tree	k-nearest neighbour
Misclassification error	0.2539	0.2139	0.4395	0.2975
Accuracy	0.7461	0.7861	0.5605	0.7025
Specificity	0.4536	0.5572	0.4500	0.6500
Sensitivity	0.8403	0.8598	0.5956	0.7297

4.3.2 Detection of Diabetic Retinopathy and Maculopathy in Eye Fundus Images Using Fuzzy Image Processing and Retinal Structures Segmentation (System VII)

System VII implements a combination of fuzzy techniques for image preprocessing, such as fuzzy filtering and fuzzy histogram equalisation. In addition, the proposed system implements the localisation and the detection of four retinal structures, which are the optic disc, the blood vessels, the macula and the fovea, which are important in the identification of maculopathy. Furthermore, the system detects diabetic retinopathy lesions, the exudates, which are vital in the detection of exudative maculopathy. Several features extracted from the exudates lesions and from the maculopathy are used for classification. The system is evaluated with a combination of normal and diabetic retinopathy images, including the maculopathy fundus images from the new dataset developed, as discussed in Section 3.9.

The proposed diabetic retinopathy and maculopathy detection system has been created using the Matlab R2014a environment. The system starts with the image acquisition process, where the system selects images from the folder for further processing. Next, the image preprocessing task takes place in order to improve the image quality. This task includes the implementation of the fuzzy image processing techniques and the retinal structures' localisation and segmentation. In order to detect the maculopathy, the lesions called exudates must be identified (where exudates situated in the macula region represents the exudative maculopathy). Several features are then extracted from the preprocessed image. Finally, in the classification phase, several machine learning classifiers, such as the k-nearest neighbour, support vector machines and Naïve-Bayes classifiers are trained using the generated features in order to classify the images into their respective classes. Figure 4.21 shows the block diagram of the proposed system for automatic screening and classification of diabetic retinopathy and maculopathy in retinal images using fuzzy image processing techniques. The individual stages are discussed in more detail in the following sections.

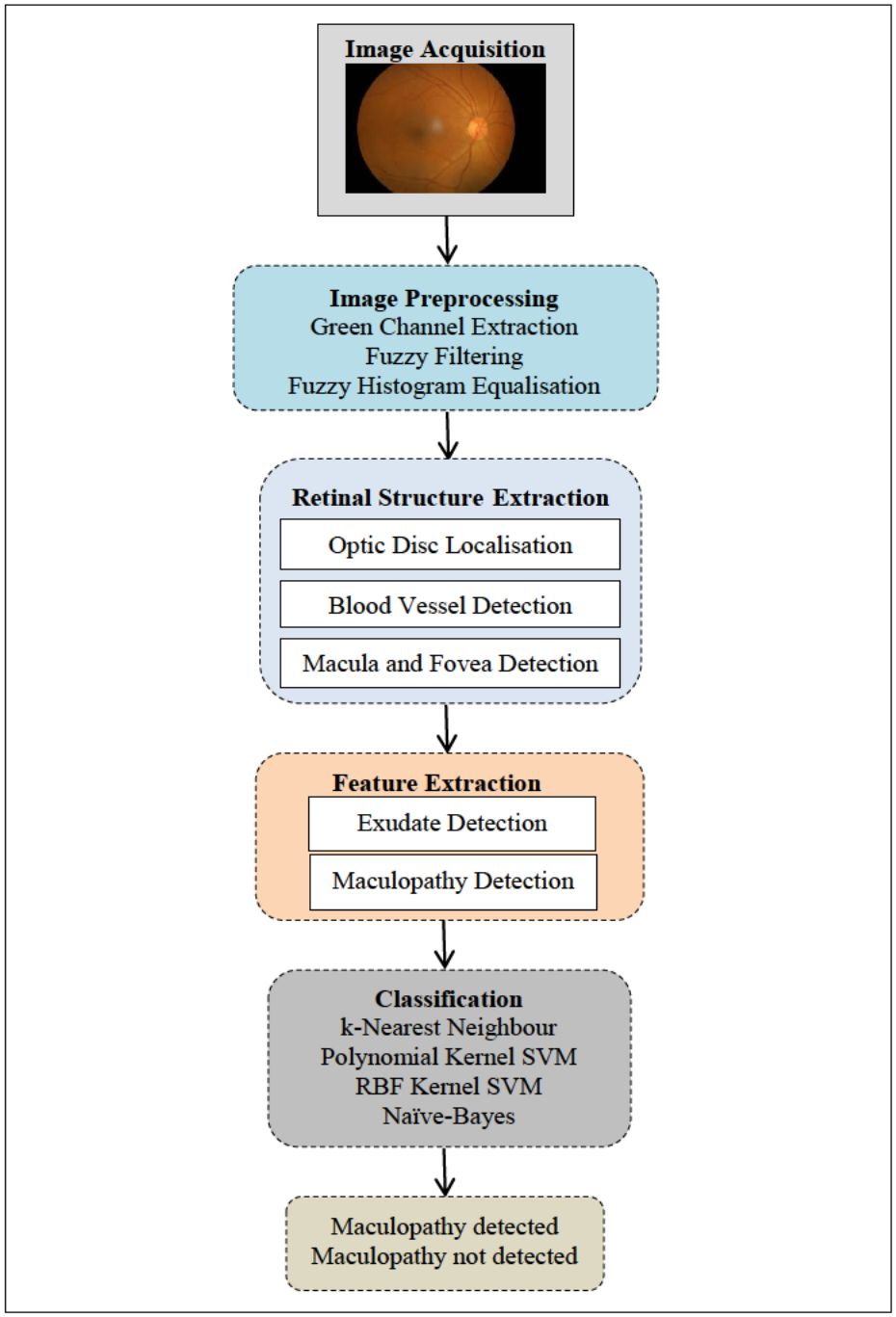


Figure 4.21 Block diagram of System VII for the automatic detection of diabetic retinopathy and maculopathy using fuzzy image processing

4.3.2.1 Image Preprocessing

Image preprocessing takes place after the image acquisition process in order to improve the quality of the image. The present system utilises the following image preprocessing

techniques: green channel extraction, fuzzy filtering and fuzzy histogram equalisation. Figure 4.22 shows the output image obtained after the preprocessing stages.

The first preprocessing technique is the extraction of the green channel from the colour fundus image, which consists of the red, green and blue channels. In the previous proposed systems (System I – System VI), the colour fundus images are converted into a greyscale image. In the present system, the green channel extraction is used to investigate the difference and capability of the green channel format compared to both the greyscale format and other image colour conversion formats. In most of the research that has been carried out in diabetic retinopathy screening, the green channel is used for detecting the diabetic retinopathy lesions such as haemorrhages, vessels and microaneurysms. The red channel is somewhat saturated while the green channel contains more structural information. Therefore, it is sensible to use the green channel for the segmentation or morphological operations, since most of the image processing tools work for greyscale only. Due to the capability of the green channel, the colour fundus image is converted into the green plane channel. In addition, the aim of the conversion is to investigate the ability of colour features, as one of the features to be used for classification besides shape and intensity features. The next pre-processing techniques are performed on the green channel image.

Image filtering needs to be implemented to improve the image quality or restore the digital image which tends to have a variety of noise types. The poor photo quality may also be due to equipment related factors, such as a dirty lens or a dirty computer screen. In addition, distractions from the surroundings, such as too bright a room can be a factor in generating poor quality fundus photographs. The filtering process therefore is necessary to overcome this problem and to enable the image for further processing and for effective grading task. The proposed system implements the median filter with fuzzy techniques described by Toh et al. (2010) termed the Noise Adaptive Fuzzy Switching Median (NAFSM) filter. Although the proposed technique is not working well as an individual system variant in System V for microaneurysm detection, the technique has been working well in System VI for both diabetic retinopathy and maculopathy detection.

After filtering the image from any noise, the third preprocessing technique, the fuzzy histogram equalisation, is performed on the images. The role of the histogram equalisation is to improve the contrast of the image. As stated above, colour fundus images are more challenging compared to angiography and red-free modes of fundus photography examination. The implementation of the histogram equalisation by employing fuzzy techniques therefore helps to improve the contrast of the fundus images for better visualisation and detection. The technique called Brightness Preserving Dynamic Fuzzy Histogram Equalisation (BPDFHE) proposed by Sheet et al. (2010) was found to work well on colour fundus images (see System IV- System VI) and has also been chosen as a preprocessing technique in this proposed system.

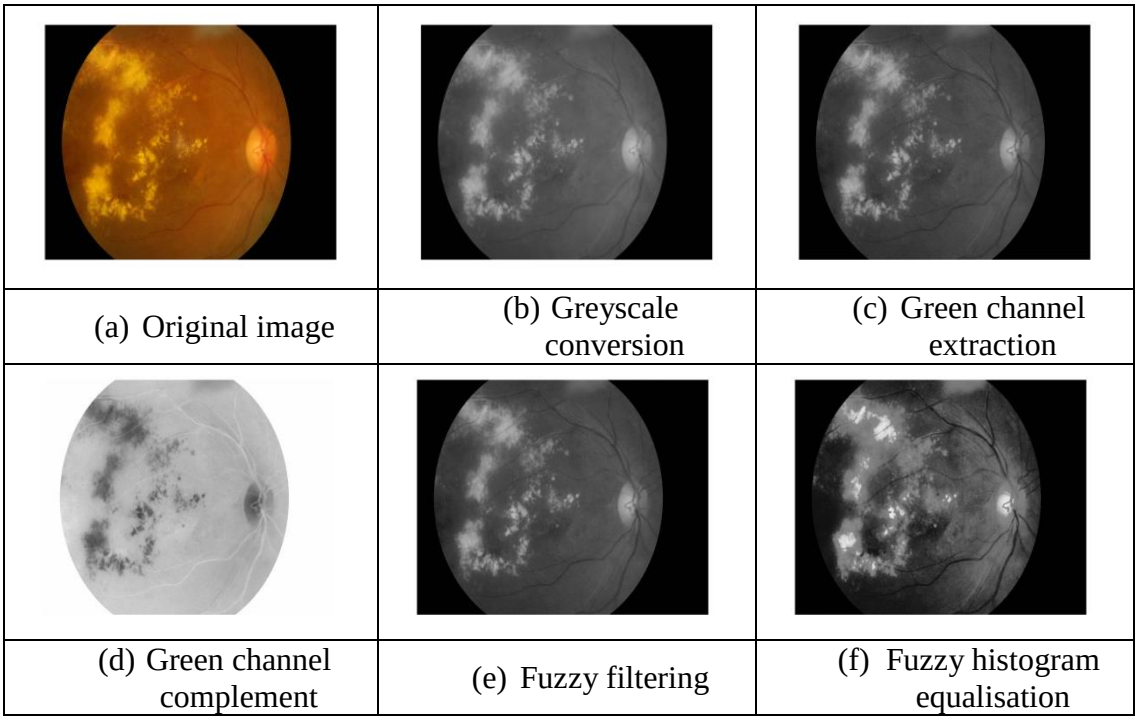


Figure 4.22 Preprocessing the output image

4.3.2.2 Retinal Structure Extraction

The extraction of retinal structures assists the diagnosis of eye diseases, through improving both the detection results and grading for lesions. The detection of retinal structures for diabetic retinopathy screening therefore, such as the optic disc, blood vessels, the macula and the fovea are essential in order to produce a reliable screening system. Figure 4.23 shows the output image with the extraction of retinal structures.

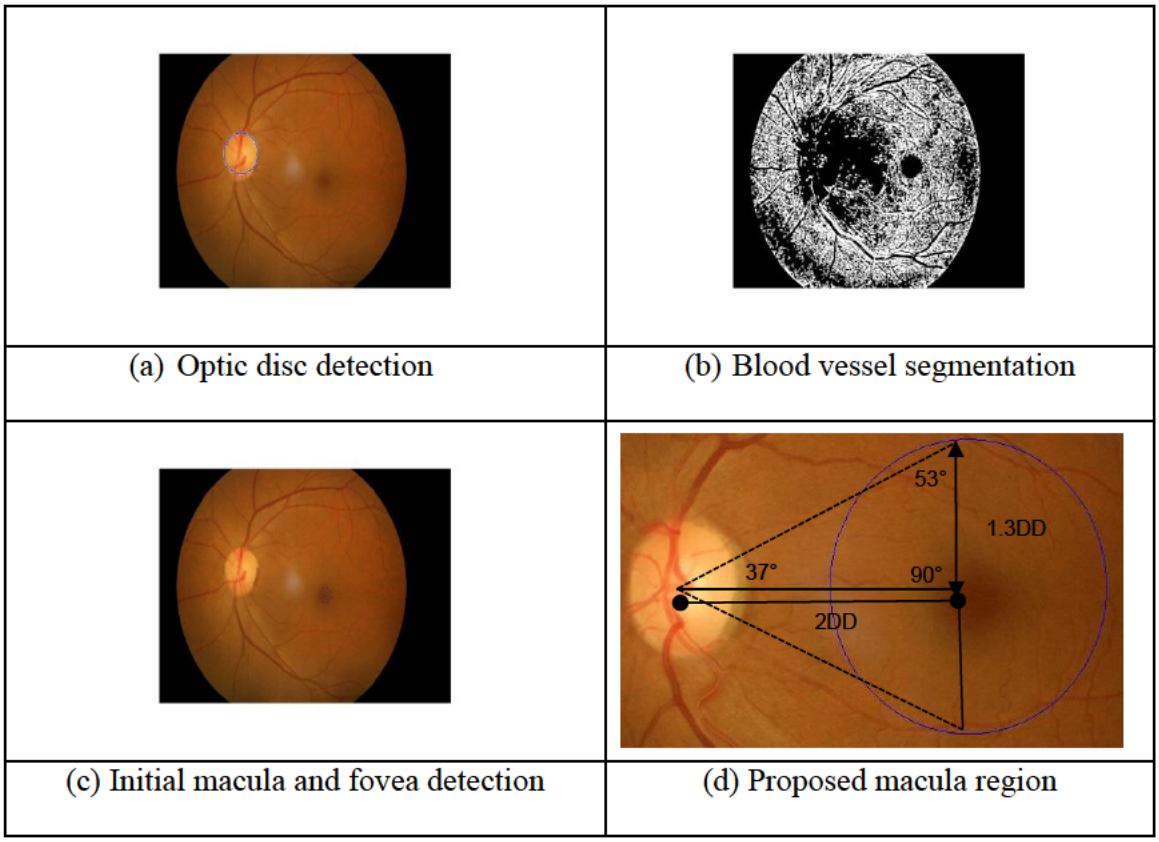
The optic disc is the most important retinal structure in the screening of diabetic retinopathy. The optic disc has the largest high contrast among all the circular shape areas. The location of the optic disc is of critical importance in retinal image analysis and is required as a prerequisite stage in detecting lesions, including exudate detection. Optic disc localisation and segmentation therefore are both performed in the proposed system in order to improve the overall detection accuracy. The technique used in the proposed system is based on the circular Hough transform (CHT), to ensure more reliability in the optic disc detection task. In this case, the Hough transform for circles is used to locate the optic disc, due to its circular shape. Based on a specified radius range, the system finds circles in fundus images using CHT with the use of the *imfindcircles* function in Matlab. After finding the circles in the image based on the radius range, the function *viscircles* in Matlab is then used to create a circle. The function draws circles with the specified centre and radius onto the current axes on the fundus images. The CHT technique has also been used for the detection of microaneurysms in Systems III and V, as this technique is works well in detecting circular shapes. In addition to the proposed CHT technique, the polygonal Region of Interest (ROI) technique can be performed on the fundus image to detect the optic disc. A region of interest is a portion of an image for filtering purposes and also for performing other operation. In order to implement this method, the *roipoly* Matlab function is used, which aims to create an interactive polygon tool associated with the image displayed in the current image, known as the target image. The function *roipoly* works by selecting vertices of the polygon and, as a result, it returns a binary image that can be used for masked filtering. The function allows moving, deleting or resizing the polygon as well as moving, adding or deleting a vertex and also changing the colour of the polygon.

After locating the optic disc, another important retinal structure represented by the blood vessels, is then extracted. There are several vessel extraction techniques including: morphological operations, the Kirsch filter, the Frangi filter, local entropy and entropic thresholding. For the proposed system, morphological operations are implemented for the extraction of the blood vessels. The operation starts where the fuzzy histogram equalisation output image is opened, using a disc shaped structuring element. The image background is then removed and the image is thresholded to obtain

the binary images containing the vessels. Finally, the morphological open is implemented using the *bwareaopen* function to remove any small noise. In order to generate the elimination of the vessels, the binary image can be subtracted from the Gaussian filtered image so that the final image has vessel free candidates.

The detection of the optic disc is vital for the detection of macula because its centre can be used for macula detection. The macula appears as a dark region near the centre of the image and its location is at a two-disc-diameter distance from the optic disc. The fovea is the centre of the macula. Once the macula is identified, it is simple to determine the fovea as its centre. The macular region can then be defined using two clinical approaches. The first approach uses the Early Treatment Diabetic Retinopathy Study (ETDRS), which indicates the presence of clinically significant macular edema (CSME) as any part located within one disc diameter of the centre of the fovea (Wilkinson et al., 2003). The second approach is based on the anatomical characteristics, where the macular region is about 5-5.5 mm in diameter. In the proposed system, three methods for macula detection are implemented. The first method uses the centre of the optic disc identified by the circular Hough transform. The macula is identified based on the distance specified from the optic disc. Once again, the circular Hough transform is used to create a circle for the macula region. The detection of the macula region is proposed by an angle of 37 degrees above and below the horizontal line crossing the optic disc centre and with the centre of the macula region situated at 2 disc diameter (2DD) distance from the optic disc centre. A circle of 1.3 discs diameter (1.3DD) is then cropped to find lesions in the macula region. Figure 4.23(d) illustrates this process more clearly. The cropped macula region can be used to locate larger and more appropriate lesion areas relevant to maculopathy. The *poly2mask* function can be used to find the region of interest of the macula region. In addition, the *imcrop* tool can also be used. However, the cropping process has its limitations as it can be performed with rectangular shapes only. This is because images are represented as arrays in Matlab and arrays are required to be rectangular. The circular region of interest (ROI) cropping can also be implemented with *roicirclecrop* function. The function crops the ROI in the form of a circular shape and with a black background based on two points: the centre and the radius of the circle.

The second method, for images with the macula as centre view, involves finding the centre of the image, where the macula is located in the centre of the retina. The parameters of the circle, such as its location and radius size are initialised, followed by creation a circle mask in the image. The masking technique is performed later where the original image is masked with the circle in order to isolate the macula part of the image. Finally, the image masked with a circle is displayed as the macula output. In order to calculate the features of the output image, the current image is changed to a binary image. The white pixels around this region are presented as maculopathy. The morphological operations can also be implemented as another of the ways to detect the macula. The top-hat transformation consists of the morphological opening of the image. The subtraction of the result from the original image operations are implemented, followed by the adding of the original image to the top-hat filtered image, and finally the subtraction of the bottom-hat filtered image. As a result, the macula is detected.



(a) Optic disc detection

(b) Blood vessel segmentation

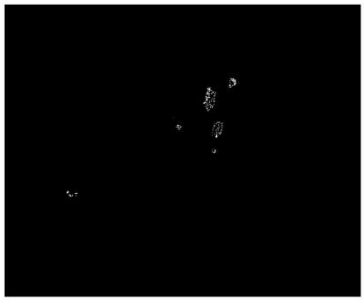
(c) Initial macula and fovea detection

(d) Proposed macula region

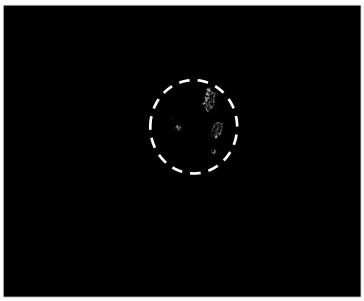
Figure 4.23 Extraction of retinal structures

4.3.2.3 Exudate and Maculopathy Detection

In order to detect maculopathy, exudates first need to be detected in the macula region. The thresholding method is one of the ways to detect the exudate lesions. Thresholding is used to extract an object from its background by assigning an intensity value (threshold value) for each pixel, such as whether the pixel is classified either as an object pixel or a background pixel. In this case, thresholding is used in the system development as the simplest form of segmentation in order to segment the fundus image into either an exudate or a background region. In the proposed system, the global thresholding or fixed thresholding is implemented, as it is one of the more popular methods. In global thresholding, the threshold value, *T*, is held constant throughout the image. Choosing a correct threshold value is quite challenging and it is important to ensure that the chosen value is neither too low nor too high. In order to find a suitable threshold value for this system development, software termed ImageJ (ImageJ, 2014) is used (through using the thresholding slider bar from the Adjust Threshold menu). From the observations and the threshold value found during the searching process, it is concluded that a value of 135 is the most appropriate in order to segment both the exudate regions and the background of the fundus images, obtained after the fuzzy histogram equalisation task. In addition to global thresholding, Fuzzy C-Means (FCM) clustering can also be implemented in the system for detecting exudates. Morphological operations can also be used for the extraction of exudates. The image after the optic disc localisation and the segmentation of the blood vessels is then generated for the feature extraction task, which will later be converted into a binary image in order to extract the features of the exudates. After the detection of the exudates, the maculopathy can be identified by cropping the area around the macula region. Figure 4.24(a) shows the exudates extraction with the optic disc overlay, while Figure 4.24(b) shows the maculopathy output within the proposed macula region.



(a) Exudates detection



(b) Maculopathy detection

Figure 4.24 Exudates and maculopathy extraction output image

4.3.2.4 Features Extraction

After performing the preprocessing techniques, the retinal structure extraction and also the exudates detection, feature extraction then takes place in order to obtain the features from the given images. There are three features selected from the exudates output image and macula image, respectively. They are the area of on pixels, the mean of on pixels and the standard deviation of the on pixels for the exudates region. In addition, there are another three features from the maculopathy region, i.e., the area of on pixels, the mean of on pixels and the standard deviation of the on pixels for the maculopathy. These shape-values are chosen as they are suitable for representing the exudate and maculopathy regions. Since the pre-processing techniques are performed after the conversion of colour fundus images into the green channel, it can be concluded that the system also investigated the capability of the colour-based features as well. The difference between the mean pixel values for the exudate and maculopathy regions and between the standard deviations of pixel values for the exudate and maculopathy regions are explored. The features between the exudates region and the maculopathy region are then compared. The value of the exudates area is higher compared to the area of the maculopathy value as the maculopathy is located around the macula, and the diameter of the macula is small.

4.3.2.5 Classification

The six extracted features were used in the classification stage. As the system focuses on the detection of maculopathy, the classes from the developed dataset, as presented in Table 3.2 above (in Section 3.9), have been categorised into two classes, which are: maculopathy detected or eye fundus with maculopathy (131 images) and maculopathy not detected or fundus without maculopathy (469 images). Several machine learning algorithms, such as the 1-nearest neighbour classifier, Naïve-Bayes classifier, support vector machines (SVM) and radial basis function kernel SVM, have been selected to train and classify images into their respective classes.

4.3.2.6 System Results and Evaluation

Figure 4.25 shows the user interface snapshot of the proposed system. The results are shown in Table 4.10. The confusion matrix, the sensitivity, the specificity and the accuracy of the individual classifiers are presented. Since the maculopathy detected class (131 images) is imbalanced compared to the maculopathy not detected class (469 images), the maculopathy detected class was oversampled several times. As a result, a total of 990 images, consisting of 469 images from the maculopathy not detected class and 521 images from the maculopathy detected class are involved in the final classification stage. The new dataset is split randomly into 90% for training and the remaining 10% for testing purpose. The process is repeated ten times in a cross-validation procedure to generate unbiased results. The results are averaged over ten runs for each of the classifiers. The experimental results show that the four classifiers are able to identify well for both categories, in particular the k-nearest neighbour and radial basis function kernel support vector machine. The prior detection of exudates is important because their presence will determine the whether or not maculopathy is present. Based on the results presented, it can be seen that the sensitivity value is a little lower than the specificity. This is due to the fact that the total number for maculopathy detected (abnormal) cases is lower than the total number for maculopathy not detected cases (normal), which was explained above. The other reason may be the capability of the global thresholding technique which was used for the detection of the exudates. The proposed threshold value may be quite high and, as a result, some of the exudates may not be detected by the proposed technique.

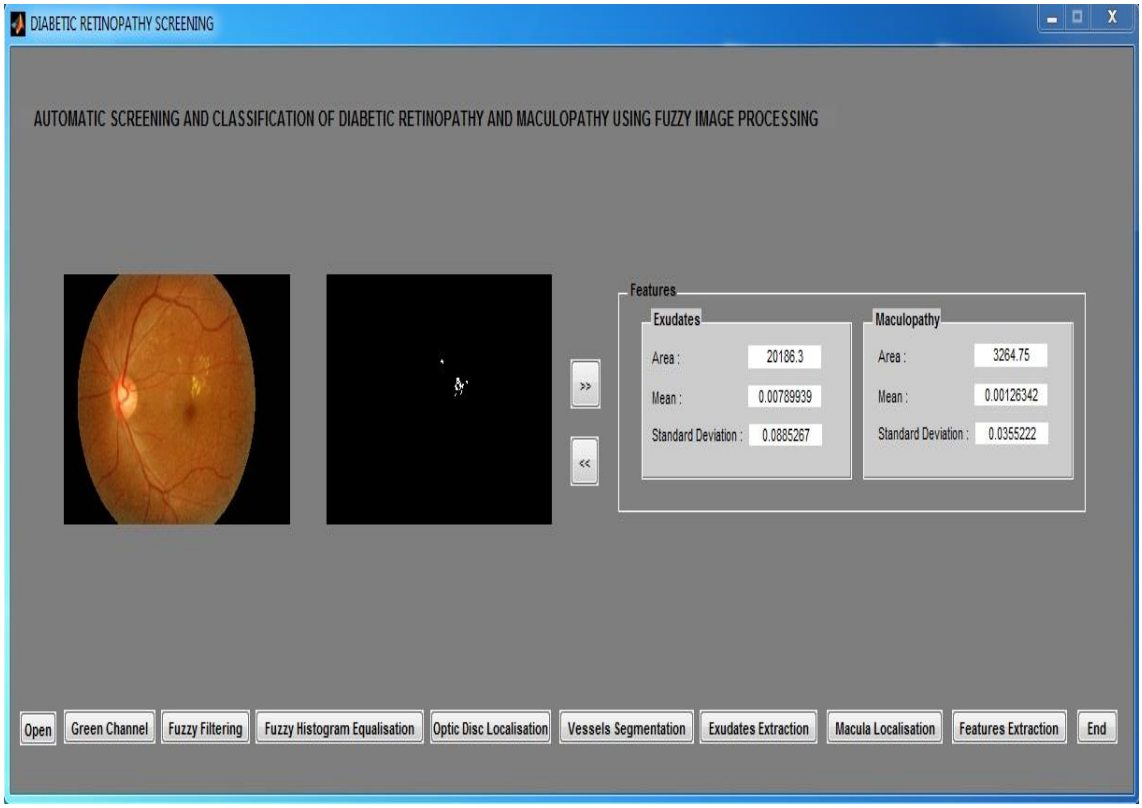


Figure 4.25 Snapshot of the proposed system user interface

Table 4.10 Average results when using the four classifiers

	k-nearest neighbour	Polynomial Kernel SVM	RBF Kernel SVM	Naïve-Bayes
Misclassification error	0.0700	0.3000	0.0700	0.2500
Accuracy	0.9300	0.7000	0.9300	0.7500
Specificity	1.0000	0.9787	0.9362	0.9149
Sensitivity	0.8679	0.4528	0.9245	0.6038

4.4 Summary

A preliminary system for the detection of diabetic retinopathy using a combination of non-fuzzy techniques is presented in System I. Several individual systems for the automatic detection of microaneurysms in colour fundus images for diabetic retinopathy screening are also presented in Systems II to V. System II highlights the automatic detection of microaneurysms in colour fundus images using segmentation and feature extraction. Two subsystems for an automatic detection of microaneurysms in colour

fundus images using the Circular Hough Transform method for the localisation of microaneurysms have been proposed, due to the capability of the proposed method to detect circular shapes. The first subsystem proposed a combination of image processing techniques and Circular Hough Transform, while the second subsystem presented the detection of microaneurysms using fuzzy image processing. The first system, which applies a non-fuzzy technique for image preprocessing is compared to the second system, which implements a fuzzy image preprocessing technique. Based on the results obtained, it was concluded that the implementation of fuzzy preprocessing techniques provides better contrast enhancement for fundus images and in addition it can greatly assist in detecting microaneurysms. Due to promising results in the implementation of the fuzzy histogram equalisation technique for the detection of microaneurysms, the development of the microaneurysms detection system has been enhanced by developing a new dataset and using other fuzzy techniques for image preprocessing.

The implementation of separate fuzzy filtering and fuzzy edge detection, in addition to the fuzzy histogram equalisation (as discussed previously), has been proposed for the automatic detection of microaneurysms in System V. The fuzzy techniques work better for both fuzzy histogram equalisation and fuzzy edge detection. The analysis shows that the implementation of the fuzzy preprocessing techniques give better contrast enhancement in addition to other improvements, such as brightness, and improved segmentation for fundus images. The use of fuzzy image processing techniques plays an important role in producing better image quality and improved performance analysis. In addition, the capability of a combination of different fuzzy image processing techniques for the detection of diabetic retinopathy and maculopathy in eye fundus images is investigated in System VI. The proposed system implements a combination of fuzzy techniques for image preprocessing, which combine fuzzy filtering, followed by the fuzzy histogram equalisation and fuzzy edge detection. The system then classified images into two classes including ten additional classes, which provide more detail about the stages of the disease. The results show better identification of diabetic retinopathy cases from the two-class-classifiers compared to the ten classes' case. In addition, the results show that maculopathy can be seen clearly from the generated output image. Finally, System VII proposed a novel combination of fuzzy image

preprocessing techniques including the localisation of retinal structures (i.e., for the optic disc, the blood vessels, the macula and the fovea), followed by feature extraction and, finally, classification with some machine learning algorithms. To conclude, the use of fuzzy image processing together with retinal structure extraction can help produce a more reliable screening system for diabetic retinopathy.

Several methods and techniques of image processing were implemented to develop the diabetic retinopathy screening system, which were presented and contrasted in the sections above. Different techniques have been implemented for the proposed system in order to either detect general retinopathy signs (i.e., whether retinopathy is present or not), or more specific signs of retinopathy, such as microaneurysms, or maculopathy. Although detection using colour fundus images was challenging, the proposed techniques were able to improve the image contrast and eventually improve the performance of the system. In addition, different public data sets have been used, which contained a variety of colour fundus images. A good quality of available fundus images can help in the process of the localisation and detection of the signs of retinopathy.

5 OVERALL RESULTS ANALYSIS AND DISCUSSION

This research has explored the development of the automatic systems for screening and classification of diabetic retinopathy. Several systems have been successfully developed, which contribute to achieve the objectives of this research. In order to develop the system, eye fundus images are vital as an input. Therefore, sufficient good quality images are required for both the development and the system performance. A thorough system analysis and performance of the developed systems, alongside the novel dataset analysis were presented.

This chapter presents the analysis of the results involving the data and the developed systems. Section 5.1 discusses the analysis performed on the experts' diagnosis as a ground truth, including the descriptive and inferential analysis. The analysis of the developed systems is presented in Section 5.2, which consists of two types of analysis, namely the confusion matrix and statistical analysis. Meanwhile, Section 5.3 explains some important points for further discussion based on the research findings. Finally, Section 5.4 presents the summary of the chapter.

5.1 Developed Data Set Analysis

As presented in Section 3.9, 600 fundus images from 300 patients were selected together with the provided ground truth by the three experts from the Ophthalmology Department, Melaka Hospital, Malaysia. The images were classified into ten retinopathy stages, where the average from the three experts' findings was used as the final number of images for each stage. The first stage, which is normal (no retinopathy), contributes the greatest number of 276 images. The abnormal or diabetic retinopathy (DR) stage is divided into nine other stages: mild DR without maculopathy (72), mild DR with maculopathy (27), moderate DR without maculopathy (85), moderate DR with maculopathy (83), severe DR without maculopathy (23), severe DR with maculopathy (11), proliferative DR without maculopathy (6), proliferative DR with maculopathy (10) and finally, advanced diabetic eye disease, ADED (7).

The ground truth delivered by the experts can be placed into four categories. Table 5.1 shows the variety of the categorisation which can be used for system testing. The first categorisation is the original classification made by the experts, which divides into ten stages of retinopathy. The second categorisation divides into two cases, which are "no diabetic retinopathy" and "diabetic retinopathy". Meanwhile, the third categorisation consists of four cases involving stages of no diabetic retinopathy, non-proliferative diabetic retinopathy (mild, moderate and severe cases), proliferative diabetic retinopathy and finally advanced diabetic eye disease. The fourth categorisation is based on maculopathy detection, which classifies into two cases, namely maculopathy detected and maculopathy not detected.

Table 5.1 Expert diagnosis summary categorisation

Categorisation I		**Categorisation II**	
Retinopathy Stage	No. of Images	Retinopathy Stage	No. of Images
No DR	276	No DR	276
Mild DR without maculopathy	72	DR	324
Mild DR with maculopathy	27		
Moderate DR without maculopathy	85		
Moderate DR with maculopathy	83		
Severe DR without maculopathy	23		
Severe DR with maculopathy	11		
PDR without maculopathy	6		
PDR with maculopathy	10		
ADED	7		
Total	600		600
Categorisation III		**Categorisation IV**	
Retinopathy Stage	No. of Images	Retinopathy Stage	No. of Images
No DR	276	Maculopathy detected	131
Non-Proliferative DR	301	Maculopathy not detected	469
Proliferative DR	16		
ADED	7		
Total	600		600

Based on the ground truth provided by the experts, several descriptive and inferential analysis tasks using the SPSS statistical package were performed.

i. Boxplot

The boxplot is the first method of assessment performed for our analysis. It is a useful visualisation of how the data is distributed. In addition, the boxplot is able to display the distribution of the variable scale and the pinpointing of the outliers. Moreover, the boxplot shows five statistics, which are the minimum, the first quartile, the median, the third quartile and the maximum value. Figure 5.1 shows the representation of the boxplot performed on the ground truth, which involves a total of 1,800 images, i.e., 600 from each expert. It shows that for the first expert, there are several outliers, i.e., the extreme values, which do not fall within the inner fences. The outliers mean that these values are not frequent, particularly for the first expert, and that most of the time, these values are not within the normal range. Meanwhile, the dark line shows the median, which is the measure of the central tendency. It shows that for the first and third experts, the median value is 1 (no diabetic retinopathy), while for the second expert the median generated is 2 (mild diabetic retinopathy without maculopathy). The boxplot also shows the 25th percentile, representing 25% of cases or rows that have values below the 25th percentile, in addition to the 50% of the cases or rows that lie both within the box and the 75th percentile.

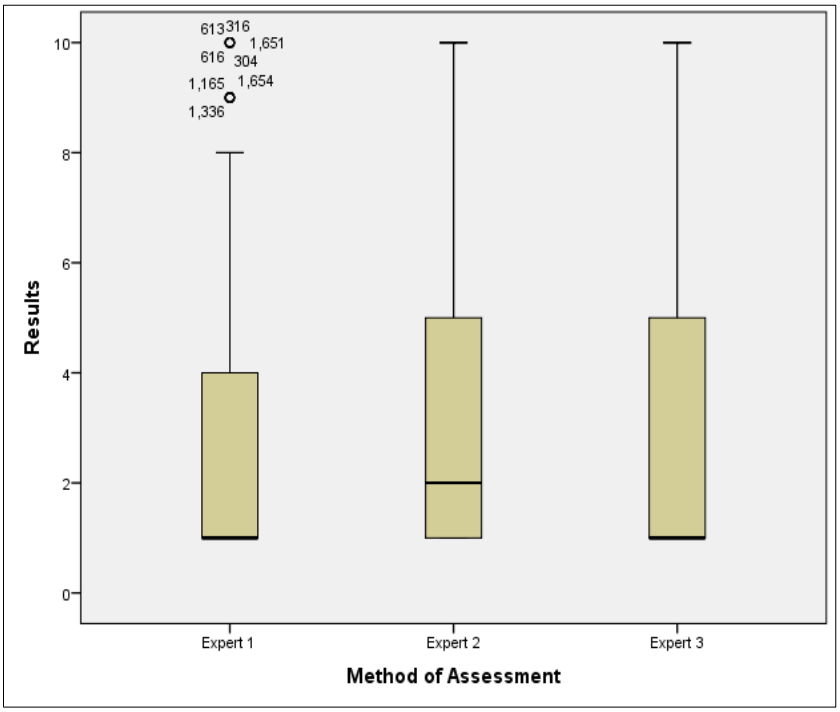


Figure 5.1 Boxplot assessment

ii. Histogram

A histogram is an alternative for a descriptive analysis that can be performed for this application. It is a visual summary of the distribution of values and it is useful for showing the distribution of a single scale variable. Figure 5.2 shows the representation of a histogram, where the 1,800 images, i.e., 600 images from each expert (600 images from the first expert, 600 images from the second expert and another 600 images from the third expert) are placed into the ten retinopathy stages. It shows that the majority of the images are classified in the first stage, which is the "no retinopathy" stage, followed by the fifth stage which is "moderate diabetic retinopathy with maculopathy". The histogram also generated the mean (2.83) and the standard deviation (2.269) for the 1,800 images used for the ground truth.

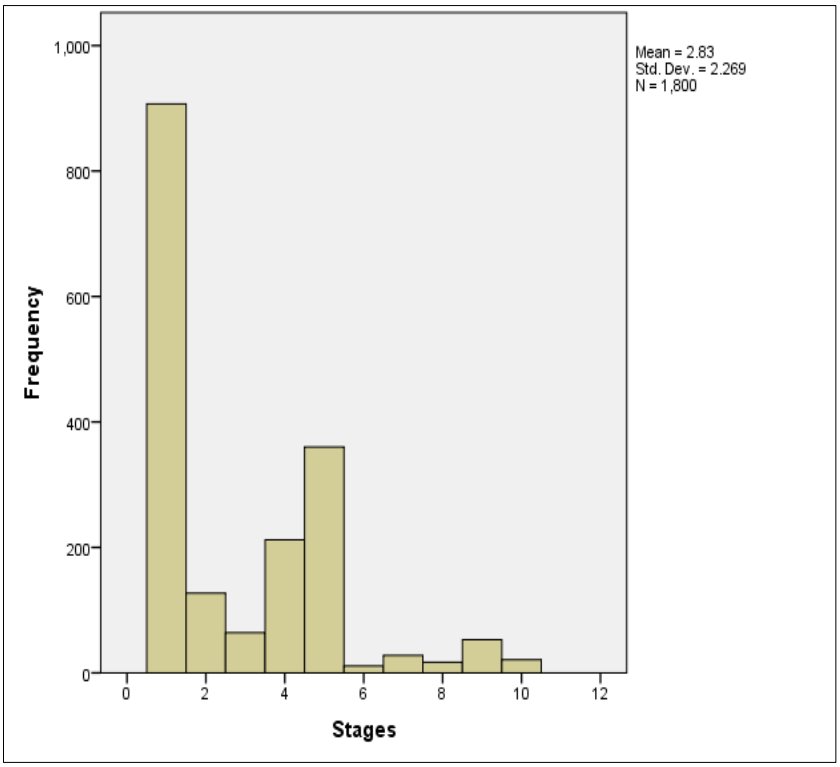


Figure 5.2 Histogram assessment

iii. Oneway ANOVA

The analysis of variance or the ANOVA test is an inferential analysis that can be performed on the expert diagnosis ground truth. The test produces a one-way analysis of variance for a quantitative dependent variable by a single factor or independent variable. The analysis of variance is used to test the hypothesis that several means are equal. The test generated shows a *p*-value of 0.000. The post-hoc test is then performed to determine which means are different. Table 5.2 presents the output of the post-hoc test, showing the multiple comparisons of the experts' means. It can be concluded from Table 5.2, that there are differences between the first expert and the second and third expert, however there is also similarity between the second and the third expert.

Table 5.2 ANOVA multiple comparisons

Method of Assessment		*p*-value
Expert 1	Expert 2	0.001
	Expert 3	0.001
Expert 2	Expert 1	0.001
	Expert 3	1.000
Expert 3	Expert 1	0.001
	Expert 2	1.000

iv. Chi-Square

The Chi-square test tabulates a variable into categories and computes a Chi-square statistic. It compares the observed and expected frequencies in each category in order to test whether or not all categories contain the same proportion of values. It can also test that each category contains a user-specified proportion of values. In this case, the Chi-square is useful for determining if there is a relationship among the experts. Table 5.3 shows the cross tabulation results of the Chi-square test. The inferential statistic with a *p*-value of 0.000 indicates that there is no relationship among the three experts. Table 5.3 represents the number of images in each category for the three experts alongside the percentage within the method of assessment (expert). The given percentage is calculated by dividing the count for each of the retinopathy stages with the total numbers of images for each expert – a total of 600 images. It can be seen that the distribution of counts and percentages for each expert for no diabetic retinopathy stage is not

significantly different. However, for mild diabetic retinopathy without maculopathy stage for example, the count and percentage for the third expert (14, 2.3%) show a significant difference compared to the first expert (55, 9.2%) and the second expert (58, 9.7%).

Table 5.3 Chi-square analysis

Results	Method of Assessment					
	Expert 1		Expert 2		Expert 3	
	Count	%	Count	%	Count	%
No DR	326	54.3	267	44.5	314	52.3
Mild DR without maculopathy	55	9.2	58	9.7	14	2.3
Mild DR with maculopathy	21	3.5	12	2.0	31	5.2
Moderate DR without maculopathy	79	13.2	90	15.0	43	7.2
Moderate DR with maculopathy	90	15.0	127	21.2	143	23.8
Severe DR without maculopathy	5	0.8	6	1.0	0	0.0
Severe DR with maculopathy	3	0.5	6	1.0	19	3.2
PDR without maculopathy	6	1.0	9	1.5	2	0.3
PDR with maculopathy	8	1.3	20	3.3	25	4.2
ADED	7	1.2	5	0.8	9	1.5
Total	600	100	600	100	600	100
p-value	0.000					

5.2 System Results Analysis

The results of the developed systems testing can be categorised into two types of analysis. A confusion matrix (contingency table) is used to define the classification model performance of test data. Meanwhile the statistical test is useful in providing a mechanism for making quantitative decisions about a process or processes.

5.2.1 Confusion Matrix

The confusion matrix is chosen as a way to represent the results to analyse the capability of the proposed system. The confusion matrix consists of information about the actual and predicted classifications, namely, true positives, false negatives, false positives and true negatives, which were explained earlier in Section 3.6 above. These values will contribute to the calculation of the sensitivity (percentage of abnormal fundus images classified as abnormal), specificity (percentage of normal fundus images

classifies as normal) and also the accuracy (overall correctness) of the proposed system. The formulas of the sensitivity, specificity and accuracy calculation are shown in Section 3.6. The confusion matrix is useful to present the classifier's ability to correctly predict or separate the classes and shows how the classification model predictions are made. Table 5.4 shows the confusion matrix analysis for the developed systems. The values of the true positives (TP), false negatives (FN), false positives (FP) and true negatives (TN) from the generated confusion matrix for the first experiment from System I (2 classes) and the first experiment from System VI (10 classes) are marked as an example for how to calculate the sensitivity, specificity and the accuracy. The TP and FN values are required for the calculation of the sensitivity, while the TN and FP values are required for the specificity calculation.

5.2.2 Statistical Analysis

In addition to the confusion matrix, a statistical test can be performed to analyse the system performance. Inferential statistical analysis, such as the analysis of variance (ANOVA) test, t-test, Chi-square and other statistical tests can be performed. The particular use of the statistical test depends on the nature of independent and dependent variables analysed, such as categorical or continuous values, in addition to the number of variables and normality. The different inferential statistical analysis presents the variation of the system results analysis. Table 5.5 summarises the statistical tests output on the developed systems results.

Table 5.4 Confusion matrix analysis of the proposed systems

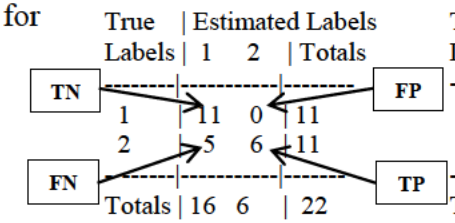
	Binary decision tree	*k*-nearest neighbour	Polynomial support vector	Radial basis support vector
System I : Preliminary system for automatic screening and classification of diabetic retinopathy				
Misclassification error	0.2091	0.01364	0.0909	0.3182
Accuracy	0.7909	0.9864	0.9091	0.6818
Specificity	1	1	1	0.5545
Sensitivity	0.5818	0.9727	0.8182	0.8091
Confusion matrix for the first experiment Labels (1: Normal, 2: DR)	 True | Estimated Labels Labels | 1 2 | Totals 1 | 11 0 | 11 2 | 5 6 | 11 Totals | 16 6 | 22	True | Estimated Labels Labels | 1 2 | Totals 1 | 11 0 | 11 2 | 0 11 | 11 Totals | 11 11 | 22	True | Estimated Labels Labels | 1 2 | Totals 1 | 11 0 | 11 2 | 2 9 | 11 Totals | 13 9 | 22	True | Estimated Labels Labels | 1 2 | Totals 1 | 6 5 | 11 2 | 2 9 | 11 Totals | 8 14 | 22
System II : Automatic detection of microaneurysms in colour fundus images using vessel segmentation and features extraction				
Misclassification error	0.0909	0.0909	0.2727	0.2727
Accuracy	0.9091	0.9091	0.7273	0.7273
Specificity	1	1	0.333	0
Sensitivity	0.875	0.875	0.875	1
Confusion matrix for the first experiment Labels (1: No microaneurysms, 2:Microaneurysms detected)	True | Estimated Labels Labels | 1 2 | Totals 1 | 3 0 | 3 2 | 1 7 | 8 Totals | 4 7 | 11	True | Estimated Labels Labels | 1 2 | Totals 1 | 3 0 | 3 2 | 1 7 | 8 Totals | 4 7 | 11	True | Estimated Labels Labels | 1 2 | Totals 1 | 0 3 | 3 2 | 0 8 | 8 Totals | 0 11 | 11	True | Estimated Labels Labels | 1 2 | Totals 1 | 1 2 | 3 2 | 1 7 | 8 Totals | 2 9 | 11

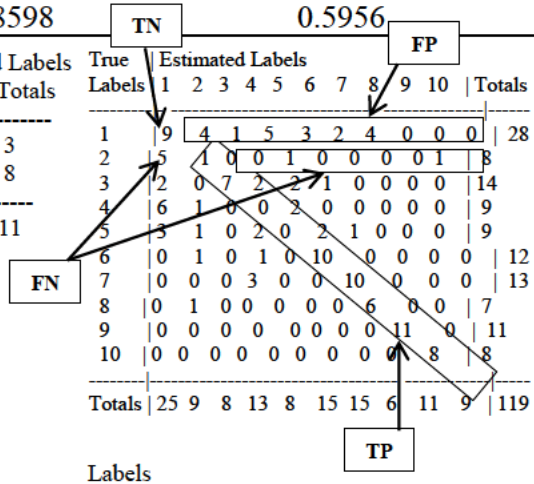
Table 5.4 (continued)

System VI : Detection of diabetic retinopathy and maculopathy in eye fundus images using fuzzy image processing				
	Category I : 2 classes		Category II : 10 classes	
	Binary decision tree	*k*-nearest neighbour	Binary decision tree	*k*-nearest neighbour
Misclassification error	0.2539	0.2139	0.4395	0.2975
Accuracy	0.7461	0.7861	0.5605	0.7025
Specificity	0.4536	0.5572	0.4500	0.6500
Sensitivity	0.8403	0.8598	0.5956	0.7297
Confusion matrix for the first experiment				

True Labels	Estimated Labels 1	2	Totals
1	3	0	3
2	1	7	8
Totals	4	7	11

Labels
(1: Normal, 2: DR)

True Labels	Estimated Labels 1	2	Totals
1	3	0	3
2	1	7	8
Totals	4	7	11



True Labels	Estimated Labels 1	2	3	4	5	6	7	8	9	10	Totals
1	9	4	1	5	3	2	4	0	0	0	28
2	5	1	0	0	1	0	0	0	0	1	8
3	2	0	7	2	2	1	0	0	0	0	14
4	6	1	0	0	2	0	0	0	0	0	9
5	3	1	0	2	0	2	1	0	0	0	9
6	0	1	0	1	0	10	0	0	0	0	12
7	0	0	0	3	0	0	10	0	0	0	13
8	0	1	0	0	0	0	0	6	0	0	7
9	0	0	0	0	0	0	0	0	11	0	11
10	0	0	0	0	0	0	0	0	0	8	8
Totals	25	9	8	13	8	15	15	6	11	9	119

True Labels	Estimated Labels 1	2	3	4	5	6	7	8	9	10	Totals
1	18	2	0	4	0	2	0	1	1	0	28
2	7	0	1	0	0	0	0	0	0	1	8
3	0	0	14	0	0	0	0	0	0	0	14
4	6	1	1	1	0	0	0	0	0	0	9
5	4	0	1	1	0	1	1	1	0	0	9
6	0	1	0	0	0	11	0	0	0	0	12
7	0	0	0	0	0	0	0	13	0	0	13
8	0	0	0	0	0	0	0	0	7	0	7
9	0	0	0	0	0	0	0	0	0	11	11
10	0	0	0	0	0	0	0	0	0	8	8
Totals	35	4	17	6	0	14	14	9	12	8	119

Labels
(1: No DR, 2: Mild DR without maculopathy, 3: Mild DR with maculopathy, 4: Moderate DR without maculopathy, 5: Moderate DR with maculopathy, 6: Severe DR without maculopathy, 7: Severe DR with maculopathy, 8: PDR without maculopathy, 9: PDR with maculopathy, 10: ADED)

Table 5.4 (continued)

System VII : Detection of diabetic retinopathy and maculopathy in eye fundus images using fuzzy image processing and retinal structures segmentation				
	k-nearest neighbour	Polynomial Kernel SVM	RBF Kernel SVM	Naïve-Bayes
Misclassification error	0.0700	0.3000	0.0700	0.2500
Accuracy	0.9300	0.7000	0.9300	0.7500
Specificity	1.0000	0.9787	0.9362	0.9149
Sensitivity	0.8679	0.4528	0.9245	0.6038
Confusion matrix for the first experiment Labels (1:Maculopathy detected, 2:Maculopathy not detected)	True Labels | Estimated Labels 1 2 | Totals 1 | 47 0 | 47 2 | 7 46 | 53 Totals | 54 46 | 100	True Labels | Estimated Labels 1 2 | Totals 1 | 46 1 | 47 2 | 29 24 | 53 Totals | 75 25 | 100	True Labels | Estimated Labels 1 2 | Totals 1 | 44 3 | 47 2 | 4 49 | 53 Totals | 48 52 | 100	True Labels | Estimated Labels 1 2 | Totals 1 | 43 4 | 47 2 | 21 32 | 53 Totals | 64 36 | 100

Table 5.5 Inferential statistical analysis of the proposed systems

	System III	System IV(a)	System IV(b)
Techniques	Greyscale conversion, adaptive histogram equalisation, circular Hough transform	Greyscale conversion, adaptive histogram equalisation, circular Hough transform	Greyscale conversion, fuzzy histogram equalisation, circular Hough transform
T-test			
p-value	0.253	0.0006	0.484
Chi-square test			
p-value	0.239	-	-
ANOVA test			
p-value	-	0.380	0.961

	System V (a)	System V (b)	System V (c)	System V (d)
Techniques	Greyscale, histogram equalisation, circular Hough transform	Greyscale, fuzzy histogram equalisation, circular Hough transform	Greyscale, fuzzy median filter, circular Hough transform	Greyscale, fuzzy edge detection, circular Hough transform
T-test				
p-value	0.00	0.92	0.00	0.73
Chi-square test				
p-value	0.00	0.94	0.00	0.81
ANOVA test				
p-value	-	-	-	-

Overall, there are seven systems developed for the detection of diabetic retinopathy, comprising one system for its general detection, four systems for the detection of microaneurysms and finally, two systems for the detection of maculopathy. Figure 5.3 represents the workflow of all the developed systems, which provides better visualisation and understanding about the developed systems proposed in this research work. Firstly, a basic system for the detection of diabetic retinopathy using a combination of non-fuzzy techniques is proposed. Next, four individual systems for the automatic detection of microaneurysms in colour fundus images for diabetic retinopathy screening are developed. The first system highlights the automatic detection of microaneurysms in colour fundus images using segmentation and feature extraction. Later, two subsystems for the automatic detection of microaneurysms in colour fundus images using the Circular Hough Transform method for the localisation of microaneurysms are proposed, due to the ability of the proposed method to detect circular shapes. The first subsystem proposed a combination of image processing techniques and Circular Hough Transform, while the second subsystem presented the detection of microaneurysms using fuzzy image processing. The first subsystem, which applies a non-fuzzy technique for image preprocessing, is compared to the second system, which implements a fuzzy image preprocessing technique. Due to the promising results in the implementation of the fuzzy histogram equalisation technique in the detection of microaneurysms, the development of the microaneurysms detection system is further enhanced by applying other fuzzy techniques in the image preprocessing of a new dataset developed at Melaka Hospital. The implementation of fuzzy filtering and fuzzy edge detection separately, in addition to the fuzzy histogram equalisation as mentioned above, are proposed for the automatic detection of microaneurysms. The capabilities of a combination of different fuzzy image processing techniques for the detection of diabetic retinopathy and maculopathy in eye fundus images was investigated (in System VI and System VII), where the proposed system implemented a combination of fuzzy techniques in image preprocessing, which combine fuzzy filtering, followed by the fuzzy histogram equalisation and fuzzy edge detection. The final system proposed a combination of fuzzy techniques for image preprocessing, in addition to the localisation and detection of four retinal structures, which are the optic disc, the blood vessels, the macula and the fovea.

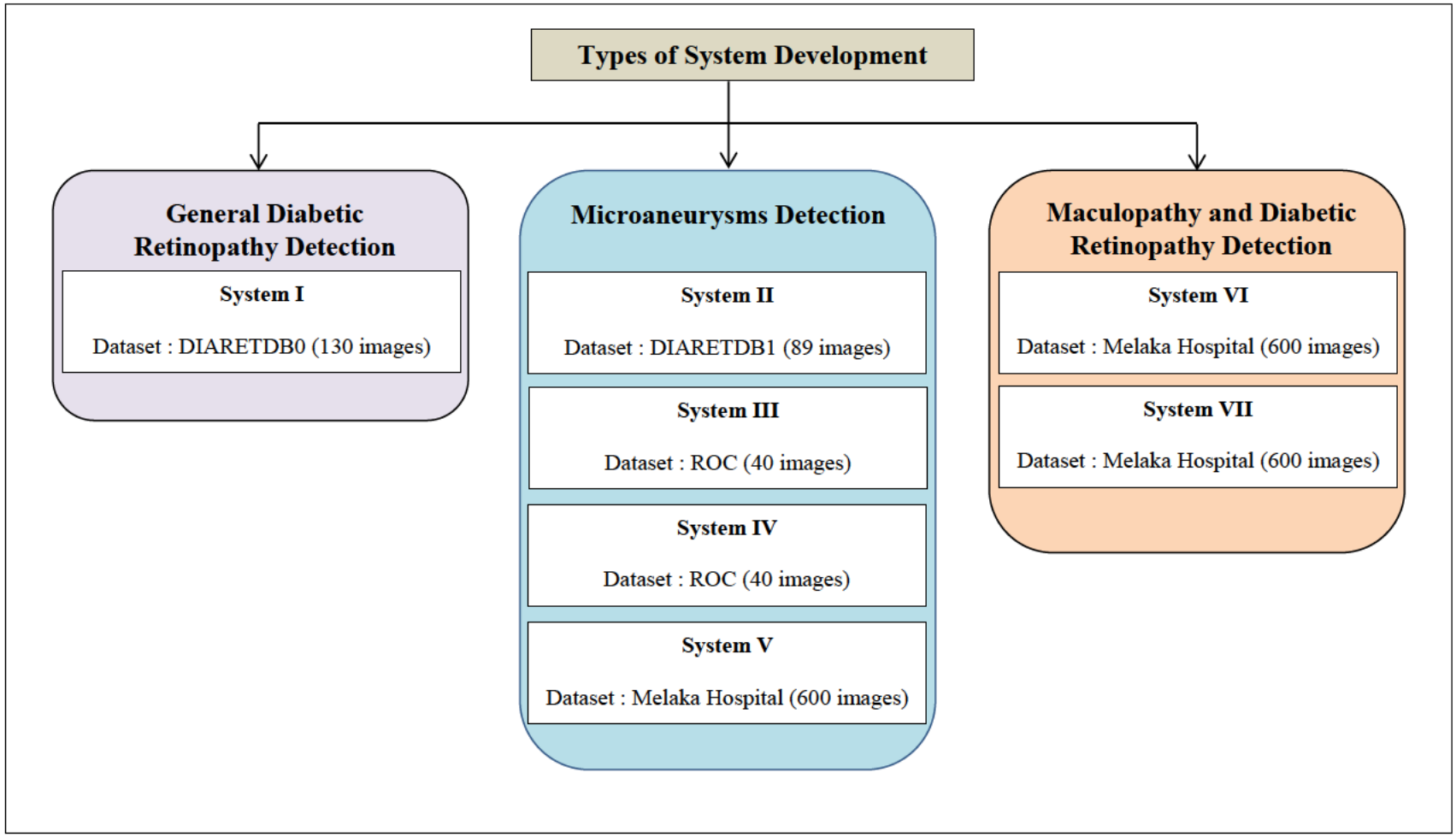


Figure 5.3 System development workflow

5.3 Discussion

The findings of this study, pertaining to the development of the effective diabetic retinopathy automatic screening and classification using eye fundus images show, some common issues:

i. Imbalanced dataset

A balanced dataset is an advantage for the purpose of classification. In the field of medical imaging however, it is difficult to achieve such a balanced dataset as there are not usually a large number of normal cases. This limitation therefore presents problems in the classification phase. For diabetic retinopathy diagnosis, this problem of imbalance also occurs in the available public databases, as stated in Section 3.8. For example, the popular dataset Standard Diabetic Retinopathy Database Calibration Level 0 (DIARETDB0), offers only 20 normal images compared to 110 images with signs of diabetic retinopathy. Meanwhile, the Standard Diabetic Retinopathy Database Calibration Level 1 (DIARETDB1) consists of only five normal images while the remaining 84 images are diabetic retinopathy case. In order to overcome this limitation, duplication is required, where the minority class is oversampled several times in order to avoid the imbalance problem. The ensemble of classifiers is another solution that can overcome the imbalanced dataset limitation.

As presented in this research work, a new dataset was introduced. The new dataset managed to overcome this imbalanced data problem, in that it provides 276 normal images and 324 diabetic retinopathy images; almost a balanced total number of No DR/Normal and DR/Abnormal images. However, the imbalance problem still occurs when dealing with the more detailed categorisation, which classifies data into ten cases (no retinopathy, mild DR without maculopathy, mild DR with maculopathy, moderate DR without maculopathy, moderate DR with maculopathy, severe DR without maculopathy, severe DR with maculopathy, proliferative DR without maculopathy, proliferative DR with maculopathy and advanced diabetic eye disease). The total numbers of severe and proliferative cases are significantly imbalanced due to the fact that in severe cases, the patient will be referred directly for laser treatment rather than

for the capturing of their fundus images. Another reason is that diabetic retinopathy takes a long time to progress to the severe stage of diabetes mellitus.

ii. Detection of exudates

As presented in Section 4.3 the localisation of exudates are important aspects to be considered for detecting maculopathy. The detection of maculopathy is based on the exudates finding, due to the fact that the maculopathy represents the exudates found in the macula region. Therefore, the detection of exudates, as an input, is vital to ensure the efficient detection of maculopathy. In addition, the fovea and the region of macula detection is another important aspect that should be accounted for.

The research work implemented a thresholding method to detect the exudate lesions in System VII. Since maculopathy detection depends on the successful location of exudates, a precise exudate detection method is required. The proposed threshold values used for the global thresholding should be both suitable and applicable to all the tested images, as each image consists of different contrast values. An inappropriate threshold value will result in a poor detection rate for exudates.

iii. Fuzzy techniques combination capability

Several fuzzy techniques have been implemented in the research work used for the automatic screening and classification of diabetic retinopathy. Among the proposed fuzzy techniques are the fuzzy histogram equalisation, fuzzy filtering and fuzzy edge detection. Fuzzy median filtering was proved not to work well individually in the detection of microaneurysms in System V(c). Fuzzy histogram and fuzzy edge detection however were proved to work well individually in System V(b) and System V(d), respectively.

On the other hand, the fuzzy median filter was working well with the combination of other fuzzy techniques, such as the fuzzy histogram equalisation and fuzzy edge detection. These combinations of fuzzy techniques were working well for the detection of diabetic retinopathy and maculopathy as presented in System VI. Other fuzzy filtering techniques should also be proposed and investigated in order to overcome the

limitations of the Noise Adaptive Fuzzy Switching Median (NAFSM) filter, which was used in the proposed system.

iv. Variety of diabetic retinopathy categorisation

It can be seen that for the diabetic retinopathy and maculopathy detection, there are two types of classification involved. The first categorisation is based on two cases, which are termed “normal” and “diabetic retinopathy”. The second categorisation is more detailed compared to the first as it consists of ten cases, i.e., No Diabetic Retinopathy (DR) and the other nine detailed cases of diabetic retinopathy: Mild DR without maculopathy, Mild DR with maculopathy, Moderate DR without maculopathy, Moderate DR with maculopathy, Severe DR without maculopathy, Severe DR with maculopathy, Proliferative DR without maculopathy, Proliferative DR with maculopathy and Advanced Diabetic Eye Disease (ADED). These two types of categorisation offer a variety of results and performance analysis of the system.

The most important reason for implementing the second categorisation (the ten cases) is in order to follow the current practice observed by ophthalmologists in the diabetic retinopathy and maculopathy classification and grading. This detailed categorisation has been acknowledged by the experts during the data collection and the ground truth preparation process.

v. Variety of system configurations

A variety of system configurations have been presented in this research work, which aim to develop an automatic screening and classification system for diabetic retinopathy, in order to reduce the workload for the screening team. It can be concluded therefore that all the proposed systems are related. The research work began with the preliminary system for automatic screening and the classification of diabetic retinopathy using fundus images. The research work continued with the detection of one of the diabetic retinopathy important features, which are microaneurysms. Since the detection of maculopathy is vital for the urgency of referral, the research work has continued with the detection of diabetic retinopathy and maculopathy based on current practice for

ophthalmologists. The earlier proposed techniques are reused for the following system configurations due to their good performance.

Other researchers focus on the maculopathy detection on the eye fundus images and suggest several solutions. They have proposed a variety of ways to detect and classify the fundus images into different stages of maculopathy, such as mild, moderate and severe maculopathy. However, this research work presented different mechanisms of maculopathy detection based on ophthalmologists' practice, which combine the detection of both diabetic retinopathy and maculopathy, based on the discovery of diabetic retinopathy signs. The severity level is based on the diabetic retinopathy features, rather than the severity of the maculopathy. The classification refers to whether maculopathy is present (with maculopathy) or not (without maculopathy). As a result, the generated cases are: No Diabetic Retinopathy (DR), Mild DR with/without maculopathy, Moderate DR with/without maculopathy, Severe DR with/without maculopathy, Proliferative DR with/without maculopathy and Advanced Diabetic Eye Disease (ADED). This categorisation is useful as two important aspects can be detected in just one screening process. Moreover, the urgency of the referral which should happen within four weeks, as presented in Table 2.14 by the National Institute for Clinical Excellence, is applied to those who have any form of maculopathy, whether mild, moderate or severe. The severity of the maculopathy is therefore not significant in this case, provided that its presence or absence has been determined.

5.4 Summary

To conclude, this chapter has discussed the analysis performed on the developed data. The overall analyses of the developed systems are also presented. Various techniques can be used to analyse the data. The confusion matrix is one of the ways to represent the performance of the classification task. It would also be useful to determine the performance of the screening system. In addition, statistical analysis is an alternative way to represent the relationship and capability of the data and the proposed system results. The chapter also presented some common issues resulting from the findings of the research.

6 CONCLUSIONS AND FUTURE WORK

The development of an automatic diabetic retinopathy screening system is a very challenging task. The system development involves not only an advanced understanding of image processing procedures, but also requires essential medical input, including expert knowledge related to diabetic retinopathy and its screening procedure, in addition to the eye fundus photography process. Efficient and cost-effective approaches in the field of digital retinal imaging should be established. Diabetic retinopathy and maculopathy screening is necessary to identify persons at risk of visual impairment. Effective screening of diabetic retinopathy therefore is vital for early action, alongside an effective diabetic complications preventive management.

This chapter concludes the thesis and provides a summary of the research. Section 6.1 reviews the performance of the research work, discusses the research contribution and further reiterates the advancement offered by this thesis. Section 6.2 presents suggestions for future research work that can provide further improvements in the field, in addition to directions for such future research studies. Finally, Section 6.3 summarises and concludes this chapter.

6.1 Review of the Work and Contributions

The automatic grading of diabetic retinopathy is a rising research field aimed to decrease the workload inherent in the conventional grading process. An automatic diabetic retinopathy system would enable faster and more efficient diagnosis. Moreover, preventive action to protect vision can be taken earlier. The output results generated from the research work have answered the primary research aim detailed in Chapter 1, where the computer-based imaging tool developed through this research has proven to be effective in detecting important diagnostic features and classifying individuals into the correct retinopathy stage.

The research main objective was to develop an automatic system for the diabetic retinopathy detection and to classify images into retinopathy stages, based on diabetic

retinopathy severity standard. In order to achieve this, the research can be summarised as follows:

i. The development of an automatic diabetic retinopathy screening system for general detection
ii. The development of an automatic microaneurysms detection system, the first important signs of diabetic retinopathy.
iii. The development of an automatic diabetic retinopathy and diabetic maculopathy detection systems.

The introductory chapter of the thesis highlighted the issues of diabetic retinopathy screening globally and in Malaysia in particular. Based on the objectives previously presented, the following represent the undertakings and the main contributions of this research:

- The research developed several systems for the automatic diabetic retinopathy detection, in addition to the identification of features of diabetic retinopathy and maculopathy lesions (Rahim et al., 2014; 2015a; 2015b; 2015c; 2016)
- The developments of the system introduced novel use of image processing techniques for the fundus images handling in the screening process of diabetic retinopathy (Rahim et al., 2014; 2015a; 2015b; 2015c; 2016)
- A new dataset of fundus images was developed, as an input for the research development, which is not only beneficial in the screening of diabetic retinopathy process, but for other retinal disease screenings, such as cataracts, glaucoma and hypertensive retinopathy among others. The new dataset is available at http://creative.coventry.ac.uk/fundus (Rahim et al., 2015b; 2015c; 2016)
- A thorough system performance analysis was undertaken, which compared the performance of automatic systems to the manual diagnosis performed by the expert

- Based on the proposed techniques and system configurations, the research designed a complete process for the automatic diabetic retinopathy screening, where the proposed system development framework can also be implemented for the automatic detection of other retinal diseases with only slightly different features involved
- The research developed several automatic detection systems for the microaneurysms, the earliest visible and most important sign of diabetic retinopathy (Rahim et al., 2015a; 2015b)
- The development of the systems employed fuzzy image processing techniques as a core contribution to the performance of the research work (Rahim et al., 2015a; 2015b; 2015c; 2016)

Results from this research will benefit a number of areas; most notably, it will significantly improve the detectability of human eye diabetic retinopathy. Preventative action therefore can be taken to decrease the rates of diabetic retinopathy problems, in addition to the blindness risk. It also aims to assist clinicians to diagnose diabetic retinopathy at an early stage by using the developed detection techniques. The decision support system for clinical diagnosis would contribute greatly in assisting with the management and detection of diabetic retinopathy. The automated system will assist an ophthalmologist (or optometrist) to detect diabetic retinopathy (and its detailed classification) in a more efficient and faster way, compared to manual analysis. In addition to the classification of diabetic retinopathy, the system will indirectly assist in the provision of recommended follow-up schedules and treatment for each category of diabetic retinopathy, based on the generated classification. The crucial aim of diabetic retinopathy is to identify any sight threatening conditions and to make sure prompt treatment in order to avoid vision loss. Such appropriate ophthalmologist referrals should therefore be facilitated with the adoption of this system.

Moreover, this research provides a significant contribution to knowledge in the area of medical image processing. This is achieved by proposing a novel use of image processing techniques in diabetic retinopathy screening, as listed in Chapter 1 and above in this chapter. The research proposes the image processing techniques combination for

the general diabetic retinopathy detection (System I). In addition, the research proposed a fuzzy technique-based eye screening system to detect the microaneurysms (System II, System III, System IV and System VI), one of the most important diabetic retinopathy signs. The developed system for the detection of microaneurysms could be a benchmark for the detection of other diabetic retinopathy signs development systems, such as exudates, haemorrhages and neovascularisation. Furthermore, the research presents a novel automatic diabetic retinopathy and maculopathy detection in retinal images using fuzzy image processing (System VI and System VII), which classifies retinopathy into stages based on the actual practice of the screening team (i.e., drawing from conventional practices). The proposed fuzzy-based image processing decision support system will help the screening of diabetic retinopathy and decrease the workload of the screening personnel.

The development of an online novel dataset, which consists of 600 colour fundus images, alongside expert diagnosis is another important contribution of the research (System V, System VI and System VII). The normal and diabetic retinopathy fundus images combination from a new dataset representing the South East Asian population, in particular the Malaysian demographic, was a major part of this research work. One significant attribute of the dataset is that unlike other publicly available datasets, it represents the Asian population, as large numbers of such data are uncommon. The developed dataset is useful for researchers in promoting research on the area of retinal-imaging, particularly in the field of diabetic retinopathy screening.

6.2 Future Work

As highlighted in an earlier section, the research work has produced several novelties that were embedded in the variants of the developed systems. Despite the fact that the promising results in the several techniques implementation showed in the this study, it is important to state that there is still room for improvement and some new directions for future research are listed below.

i. Combination of diabetic retinopathy features detection

Diabetic retinopathy screening is a complicated process, as there are various signs of that need to be identified and detected in order to achieve a complete screening system. This research study however, concentrated on microaneurysms, the earliest and the most important diabetic retinopathy signs. Other important diabetic retinopathy features, such as exudates, haemorrhages, cotton wool spots and neovascularisation also need to be identified, according to the standard clinical severity scales for diabetic retinopathy. For each of the diabetic retinopathy features listed above, novel use of techniques should be proposed for their effective detection. In addition to these features, there are some exclusion criteria that need to be considered for the task of diabetic retinopathy detection, for example polyps, bleeding and drusen. The combination of all these features of diabetic retinopathy into a single system will provide a complete automatic diabetic retinopathy detection system. The diabetic retinopathy screening process has immense scope because it involves many features and criteria that need to be taken into account. The research can be extended to identify the other remaining diabetic retinopathy features and combine them into a complete screening system. A complete and accurate system could be used to assist the team of diabetic retinopathy screening to perform in an improved and more efficient way. As a conclusion, diabetic retinopathy screening is not an easy task, as many criteria need to be thoroughly examined before any diagnoses can be made.

ii. Counting constraints for microaneurysms

The counting of microaneurysms by an expert is required for a precise analysis in the development of the system or model, in order to make a comparison between the system results and the system counting. The number of microaneurysms given by the expert for the novel developed dataset is required as an input for the statistical tests, for example the T-test and Chi-square test. However, according to the expert from the Department of Ophthalmology, Melaka Hospital, Malaysia, the microaneurysms counting is almost impossible due to the following constraints. For example, if microaneurysms are present, they are numerous in number and the counting would no longer be accurate. This is further complicated when there is some overlapping among the microaneurysms. Furthermore, another constraint is the fact that microaneurysms could be easily

confused with blot haemorrhages of about the same size. A solution would be to group the microaneurysms into two main classifications, which are “No” for microaneurysms not detected and “Yes” for microaneurysms detected. For the “Yes” choice, would be another three sub-choices, i.e., “Low”, “Moderate/Medium” and “Severe”, according to the approximate microaneurysms number estimated by the expert. If there are just a few microaneurysms detected, then it is classified as “Low”, if there are several, it is classified as “Moderate”, and if there are many, then the classification will be “Severe”. The choice of these three cases is dependent on the threshold value for each class which can be fixed in advance. Based on the three sub-choices of microaneurysms detected, fuzzy logic may be used. This approach is an alternative to overcome the constraints to the accurate counting of microaneurysms. It can be applied to a novel developed dataset, that can in turn be proposed for future use of an automatic microaneurysms detection system development.

iii. Combination of other fuzzy image processing techniques

In addition to the proposed techniques of image processing, the research can be improved by the implementation of other different preprocessing techniques combinations, including those based on fuzzy approaches. The fuzzy image processing can be applied to fully explore the variety of fuzzy techniques capabilities. In order to produce a more reliable screening system, fuzzy image processing in addition to the extraction of retinal structure can be employed in diabetic retinopathy screening. An alternative technique for the future detection of optic disc, Fuzzy Circular Hough Transform, will be implemented.

iv. Widely accessible developed dataset

The research is not merely proposing an automatic diabetic retinopathy screening detection system, but has also introduced a new dataset of eye fundus images. The new dataset would be beneficial to researchers and practitioners working in the retinal imaging area, especially the diabetic retinopathy screening field. For future work, the online dataset can be made more widely accessible by integrating the dataset with other popular databases, for example the University of California Irvine (UCI) Machine Learning Repository, among others.

6.3 Summary

One of the main health threats is diabetes mellitus, as it leads to a severe and enduring complications, as well as sight-threatening conditions. Diabetic retinopathy is a diabetes complication that affects the blood vessels damage inside the retina. Thus, both initial detection and timely treatment is essential for this retinal problem. Such an effective diagnosis and the diabetic retinopathy grading can assist in early detection of diabetic retinopathy and may decrease its prevalence. It is envisaged that a decision support system for clinical screening would contribute to and greatly assist in the management as well as the detection of diabetic retinopathy. It is also hoped that the developed detection technique will assist clinicians to diagnose diabetic retinopathy at an early stage.

This research project examined the use of fundus images and techniques of image processing to detect the diabetic retinopathy presence in the eye. This is a particularly challenging problem and this research has made novel use of image processing techniques to automatically detect the retinopathy stages. Highly efficient and accurate image processing techniques must be used in order to produce an effective diagnosis of diabetic retinopathy. As such, this research proposed a new mechanism that could provide ophthalmologists with a novel way to identify and treat those who are most vulnerable to vision loss from diabetic retinopathy. Specific image processing techniques have been proposed and developed to test the efficiency of this approach compared to others. As a conclusion, the implementation of fuzzy image processing techniques play a significant role in generating better quality of image and enhanced performance. Eventually it can contribute to producing a more reliable screening system.

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APPENDICES

Appendix A Data Collection

A.1 Data Collection Process

Eye Clinic, Melaka Hospital, Malaysia

Fundus Camera VX-10

Screening Process

This item has been removed due to Data Protection. The unabridged version of the thesis can be found in the Lancester Library, Coventry University.

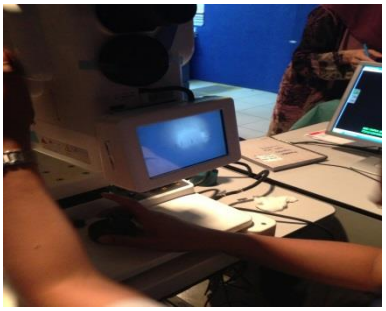


Figure A.1 Data collection and diabetic retinopathy screening process

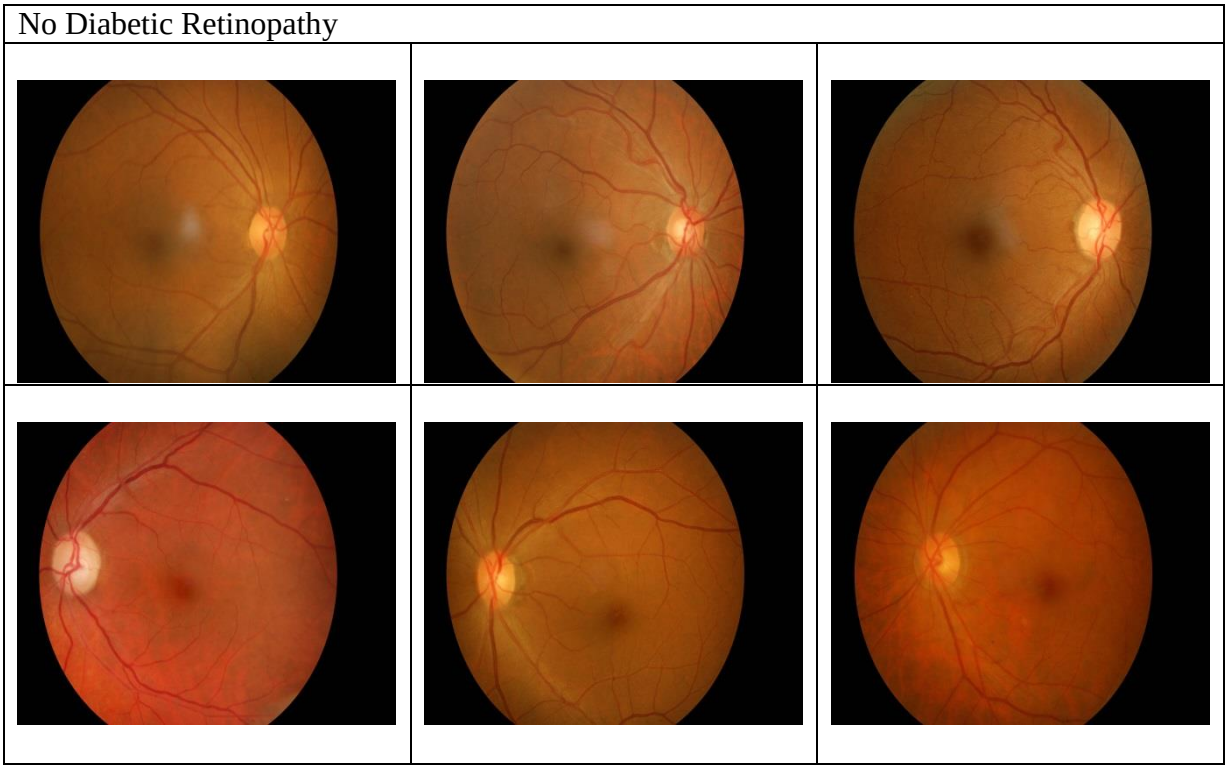


Figure A.2 No diabetic retinopathy images

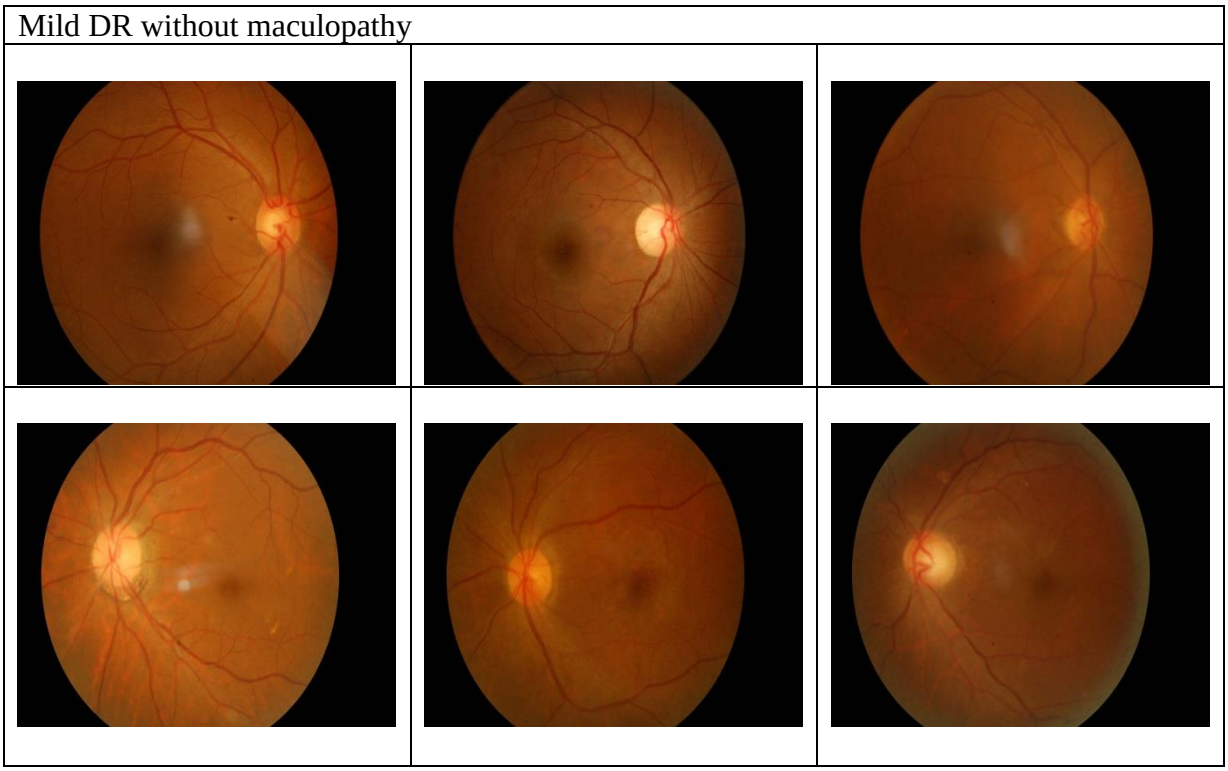


Figure A.3 Mild DR without maculopathy images

Mild DR with maculopathy

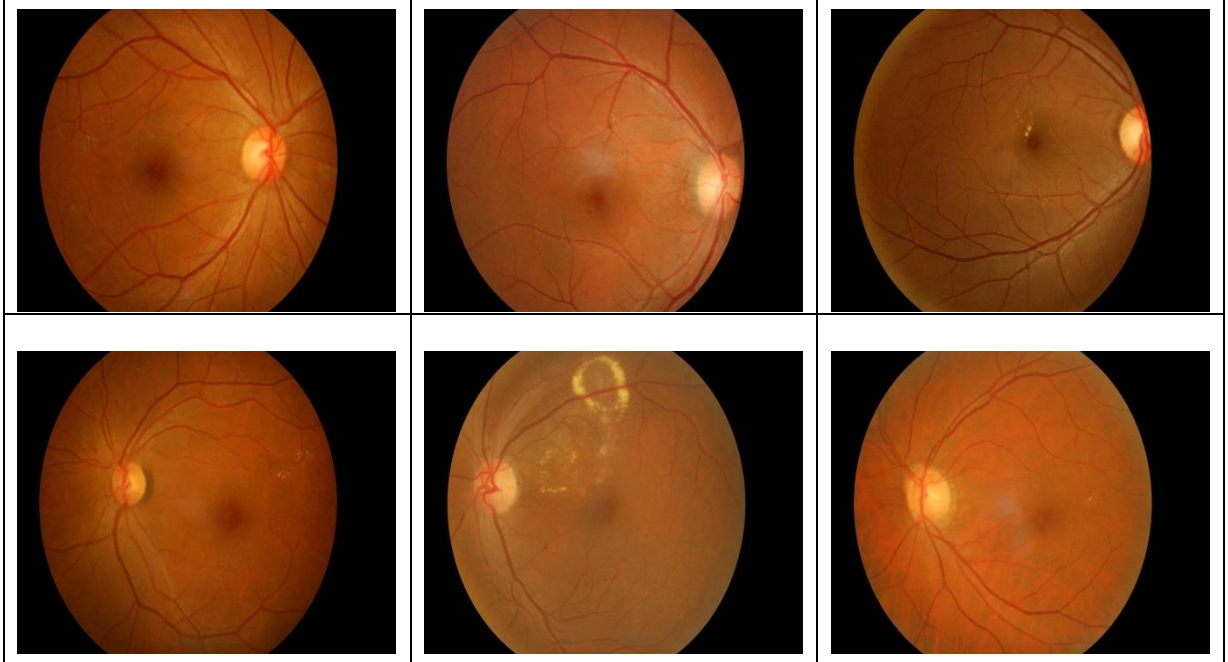


Figure A.4 Mild DR with maculopathy images

Moderate DR without maculopathy

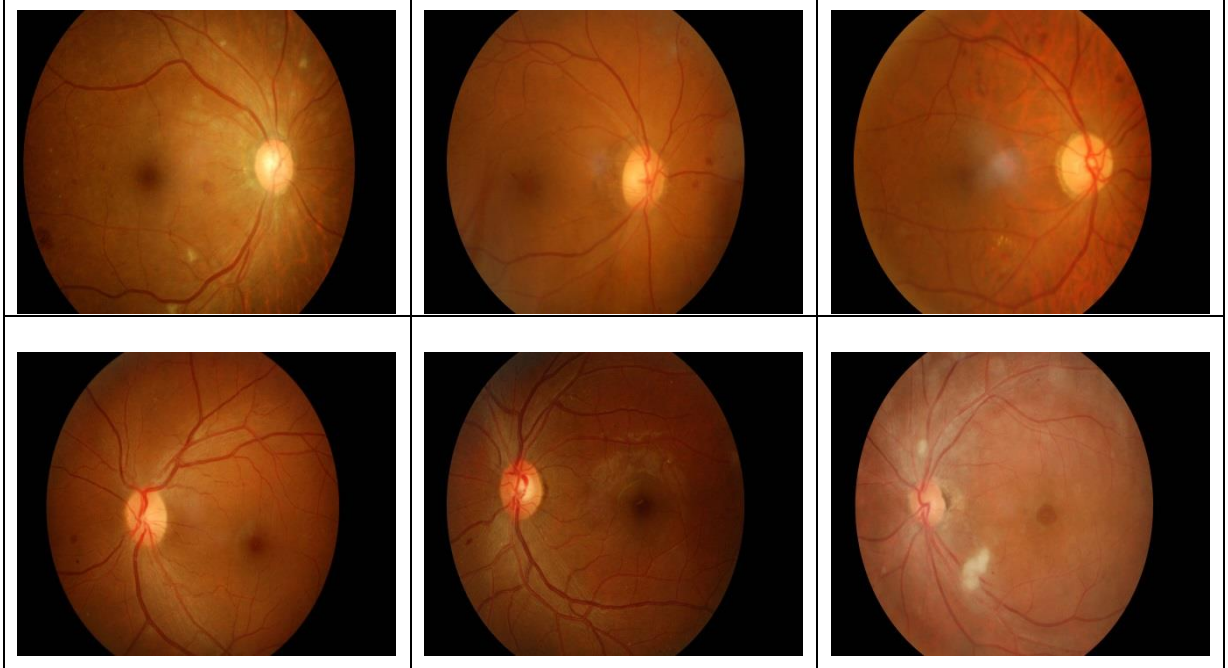


Figure A.5 Moderate DR without maculopathy images

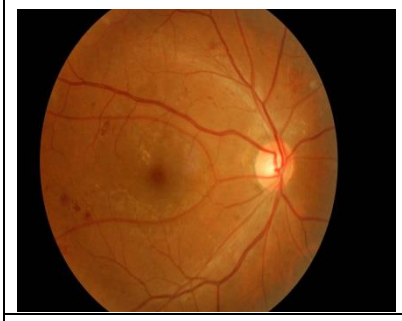
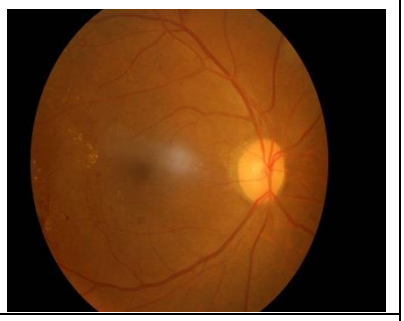
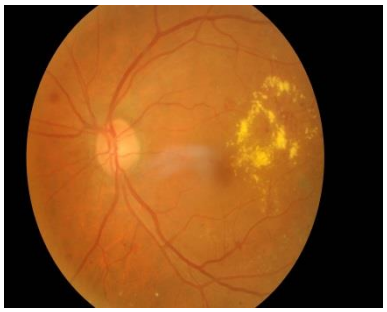
Moderate DR with maculopathy		
		
		

Figure A.6 Moderate DR with maculopathy images

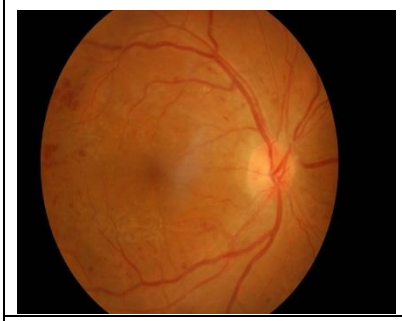
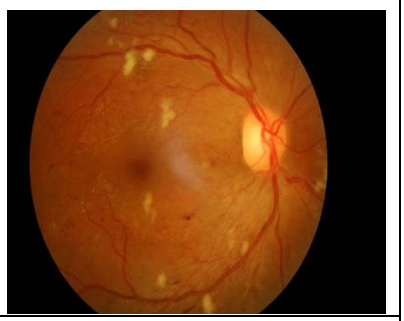
Severe DR without maculopathy		
		

Figure A.7 Severe DR without maculopathy images

Severe DR with maculopathy

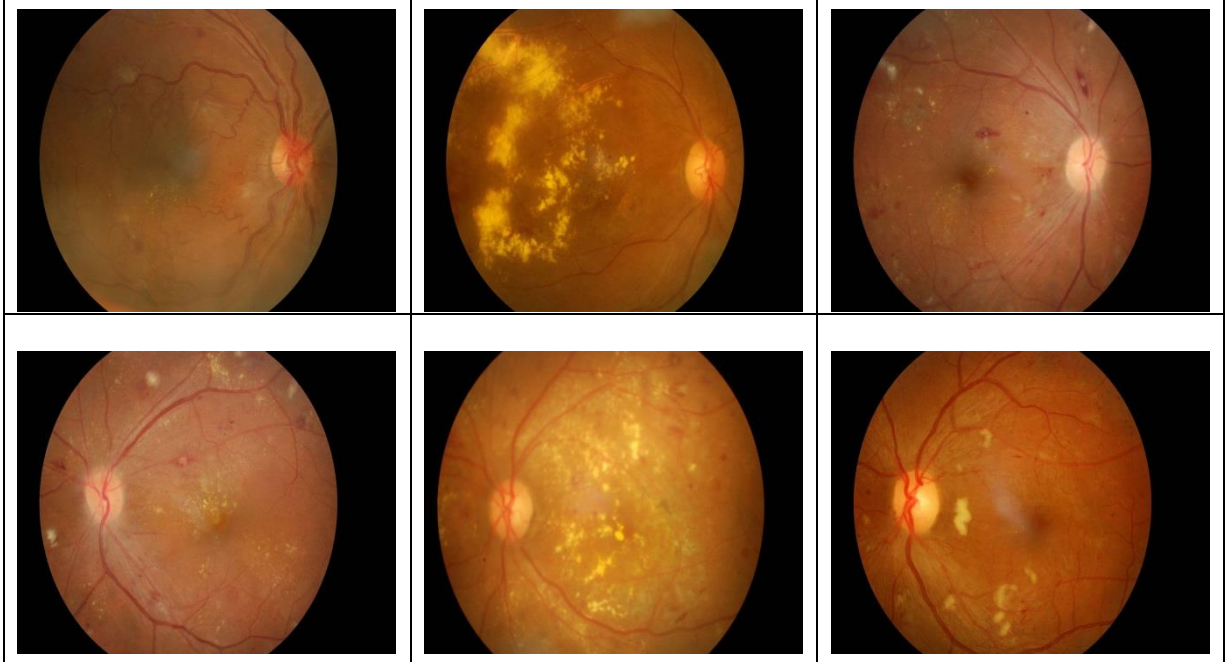


Figure A.8 Severe DR with maculopathy images

Proliferative DR without maculopathy

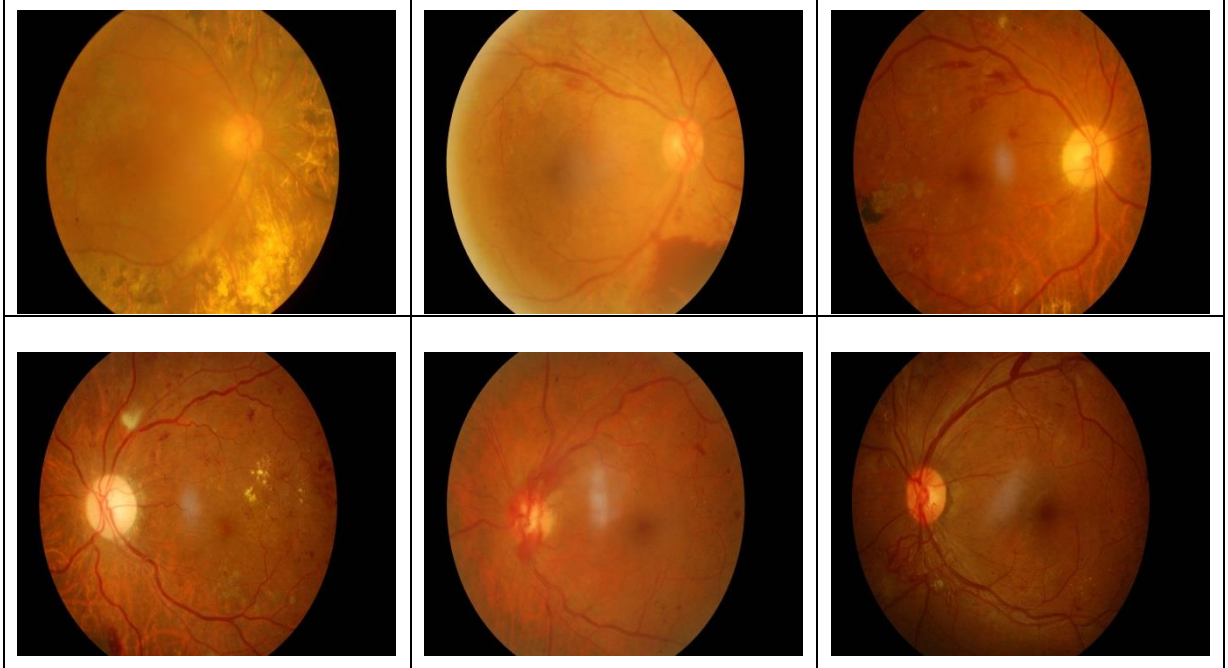


Figure A.9 Proliferative DR without maculopathy images

Proliferative DR with maculopathy

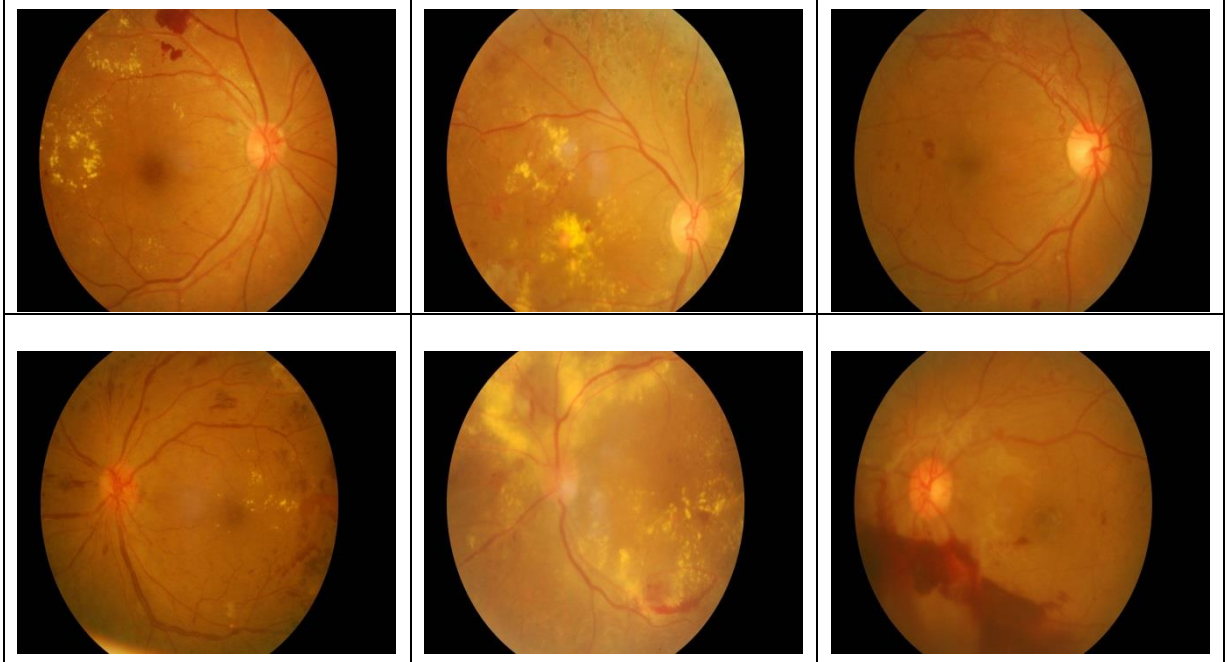


Figure A.10 Proliferative DR with maculopathy images

Advanced Diabetic Eye Disease (ADED)

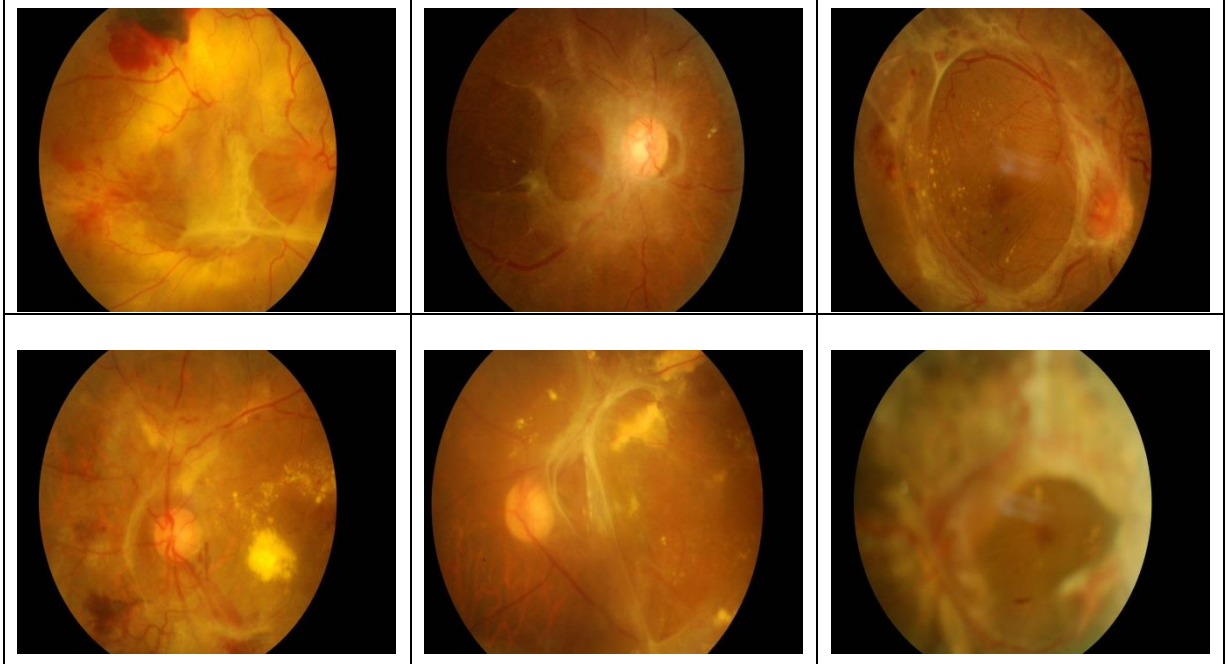


Figure A.11 Advanced diabetic eye disease images

A.2 Data Collection Summary

Table A.1 Data collection methods

Features	Description
Location	Eye Clinic, Department of Ophthalmology, Melaka Hospital, Malaysia
Duration	6 November 2014 - 30 January 2015
Data Collection Methods	i. Extracting fundus images - Copy 2401 diabetic retinopathy patient's folders from the personal computer that attached with the fundus camera into the compact discs - Information gathered from the patient's folder: • Patient Name • Patient ID • Doctor • Birth Date • Sex • Diagnosis 1 • Diagnosis 2 • Diagnosis 3 • Fundus images ii. Discussion with the ophthalmologists - Diabetic retinopathy stages - Diabetic retinopathy signs - Other diabetic retinopathy exclusion criteria - Differences between Caucasian and Asia retinal iii. Observation - Observation on the diabetic retinopathy screening process performed by the screening team - Observation on the fundus image capturing using KOWA fundus camera - Observation on the manual diagnosis by the screening team
Collection Dates	24/11/2014 : 895 patient's folders 25/11/2014 : 677 patient's folders 02/12/2014 : 458 patient's folders 16/12/2014 : 277 patient's folders 09/01/2015 : 94 patient's folders Total : 2401 patient's folders
Data Range Period	22 April 2009 to 9 Jan 2015

Table A.2 Data collection assessment

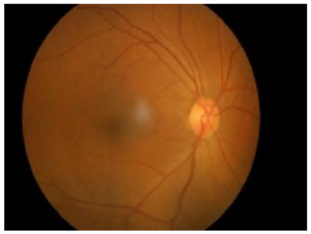
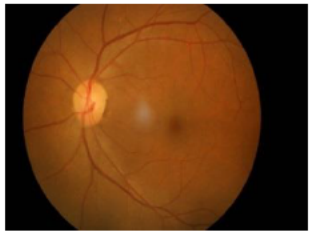
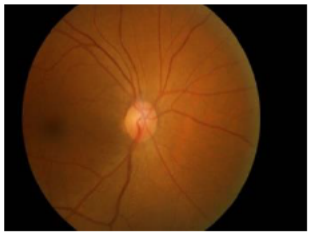
<table>
<tr><th>Features</th><th>Description</th></tr>
<tr><td>Image Capturing Procedure</td><td>Screening team will capture patient's right and left eyes and minimum 2 fundus images per patient. For each images, 2 different angles will be captured; optic disc centre and macula centre
<table>
<tr><td colspan="3">1 patient</td></tr>
<tr><td>Angle</td><td>RE</td><td>LE</td></tr>
<tr><td>Macula centre</td><td>  </td><td>  </td></tr>
<tr><td>Optic disc centre</td><td>  </td><td> </td></tr>
</table></td></tr>
<tr><td>Assessment by Experts</td><td>- 300 patient's fundus images were selected for expert diagnosis. Each patient's folders, consists of minimum one image for right eye and one image for left eye. Minimum total of fundus images selected for expert diagnosis is 600 images
- An Excel file consists fundus images link and retinopathy stages drop down list was provided to each of the experts in 3 separate thumb drives to avoid bias
- 3 experts involved for diagnosis are:
• Dr. Raja Norliza binti Raja Omar, Consultant Ophthalmologist / Head of the Department of Ophthalmology, Melaka Hospital
• Dr. Nor Fadzillah, Eye Specialist, Department of Ophthalmology, Melaka Hospital
• Dr. Alice, Eye Specialist, Department of Ophthalmology, Melaka Hospital</td></tr>
</table>

Table A.3 Expert diagnosis

Features	Description
Expert Diagnosis File	Diabetic Retinopathy Expert Diagnosis Note: Please click the Image (Column B and D) cell to view the image and Expert Diagnosis (Column C and E) cell for drop-down list. Kindly press SAVE button after enter the informations.

Patient_ID	Expert Diagnosis			
	Right Eye		Left Eye	
Patient001	image001_R_M	No DR	image001_L_M	No DR
	image001_R_OD		image001_L_OD	
Patient002	image002_R_M	No DR	image002_L_M	Mild DR without maculopathy
	image002_R_OD		image002_L_OD	
Patient003	image003_R_M	No DR	image003_L_M	No DR
	image003_R_OD		image003_L_OD	
Patient004	image004_R_M	No DR	image004_L_M	No DR
	image004_R_OD		image004_L_OD	
Patient005	image005_R_M	No DR	image005_L_M	No DR

Classification	Retinopathy stages: 10 categories No DR Mild DR without maculopathy Mild DR with maculopathy Moderate DR without maculopathy Moderate DR with maculopathy Severe DR without maculopathy Severe DR with maculopathy PDR without maculopathy PDR with maculopathy ADED

Table A.4 Expert diagnosis summary

Features	Description
Expert Diagnosis Summary	

Expert Diagnosis Summary

Patient_ID	Right Eye / Left Eye	Expert 1	Expert 2	Expert 3
Patient001	image001_R	No DR	No DR	No DR
	image001_L	No DR	No DR	No DR
Patient002	image002_R	No DR	No DR	No DR
	image002_L	Mild DR without maculopathy	No DR	No DR
Patient003	image003_R	No DR	No DR	No DR
	image003_L	No DR	No DR	No DR
Patient004	image004_R	No DR	No DR	No DR
	image004_L	No DR	No DR	No DR
Patient005	image005_R	No DR	No DR	No DR
	image005_L	No DR	No DR	No DR
Patient006	image006_R	No DR	No DR	No DR
	image006_L	No DR	No DR	No DR
Patient007	image007_R	No DR	Mild DR without maculopathy	No DR
	image007_L	Mild DR without maculopathy	Mild DR without maculopathy	No DR
Patient008	image008_R	No DR	No DR	No DR
	image008_L	No DR	No DR	No DR
Patient009	image009_R	No DR	No DR	No DR
	image009_L	No DR	Mild DR without maculopathy	No DR
Patient010	image010_R	Mild DR without maculopathy	Mild DR without maculopathy	No DR
	image010_L	No DR	No DR	No DR

Expert Diagnosis Summary

Retinopathy Stage	Expert 1	Expert 2	Expert 3
No DR	324	265	314
Mild DR without maculopathy	54	59	15
Mild DR with maculopathy	22	13	32
Moderate DR without maculopathy	83	91	42
Moderate DR with maculopathy	88	124	142
Severe DR without maculopathy	5	6	0
Severe DR with maculopathy	3	6	19
PDR without maculopathy	6	10	2
PDR with maculopathy	8	21	25
ADED	7	5	9
Total	600	600	600

Table A.4 (continued)

Features	Description
Expert Diagnosis Summary	

Image_ID	Expert_1	Expert_2	Expert_3	Overall_diagnosis	Average
image001_R	1	1	1	3	1
image001_L	1	1	1	3	1
image002_R	1	1	1	3	1
image002_L	2	1	1	4	1
image003_R	1	1	1	3	1
image003_L	1	1	1	3	1
image004_R	1	1	1	3	1
image004_L	1	1	1	3	1
image005_R	1	1	1	3	1
image005_L	1	1	1	3	1
image006_R	1	1	1	3	1
image006_L	1	1	1	3	1
image007_R	1	2	1	4	1
image007_L	2	2	1	5	2
image008_R	1	1	1	3	1
image008_L	1	1	1	3	1
image009_R	1	1	1	3	1
image009_L	1	2	1	4	1
image010_R	2	2	1	5	2
image010_L	1	1	1	3	1

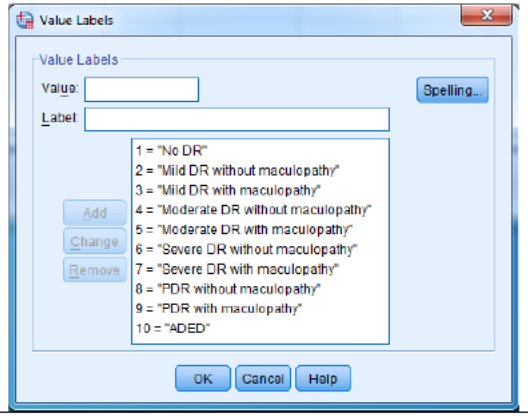


Table A.5 Findings summary

Features	Description
Findings Summary	- 3 experts involved to diagnose 300 patient's folders into 10 retinopathy stages - The findings can be categorised into 3 main distributions: No DR No DR NPDR No DR Mild DR without maculopathy Mild DR with maculopathy Moderate DR without maculopathy Moderate DR with maculopathy Severe DR without maculopathy Severe DR with maculopathy PDR without maculopathy PDR with maculopathy ADED - The total number of No DR and DR classes are mostly balance - The total number of severe and proliferative cases are hugely imbalance due to these reasons: • For severe cases, the patient will be referred directly for laser treatment rather than capturing their fundus images • The diabetic retinopathy takes a long time to progress based on the severity of the diabetes mellitus
Usefulness of the Data Set	- Representing South East Asian population, particularly Malaysian peoples - Provides mostly balance total number of No DR/ Normal and DR/ Abnormal, where in medical image database, it is difficult to find huge number of normal cases. For example: DIARETDB0 : 20 Normal and 110 DR DIARETDB1 : 5 Normal and 84 DR - The categorisation of retinopathy is following the International Clinical Retinopathy and Diabetic Macula Oedema Disease Severity Scale - Categorise into stages involving maculopathy which is the yellow lesion near the macula. The detection of maculopathy is very important as the macular is responsible for central vision and it is a sensitive part and to detect the urgency of referral. Patients with maculopathy detected need treatment and referral because it will affect the patient's vision, while patients with no maculopathy do not need referral but need to repeat fundus photography in 1 year time

Table A.6 Discussion summary

Features	Description
Discussion Summary	Discussion with Dr. Raja Norliza on the differences between Caucasian and Asian retina towards the diabetic retinopathy development: i. Pigmentation - Caucasian has less pigment ii. Colour of iris/ retinal - Caucasian has light pigment iii. Severity - Asian has more severe level of diabetic retinopathy due to: • Low control of diabetes mellitus • Foods Discussion with Dr. Nor Laila on the differences between Caucasian and Asian retina: i. Less pigment on iris - Caucasian : since has less pigment, not absorb lights point - Asian : since has more pigment, absorb all the lights ii. Eyeball axial length Caucasian : short Discussion with Dr. Raja Norliza on maculopathy: i. Without maculopathy: - No need referral - Repeat in 1 year ii. With maculopathy: - Need treatment / referral - Effect vision Discussion with Dr. Raja Norliza on Normal or No DR: i. No. DR – diabetic patients with no retinopathy signs can be a normal ii. Normal – non diabetic patients

Appendix B Online Developed Dataset Screenshots

B.1 Website Screenshots (http://creative.coventry.ac.uk/fundus)

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Figure B.1 'Home' page

Figure B.2 'About' page

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Figure B.3 'Team' page

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Figure B.4 'Publications' page

This item has been removed due to 3rd Party Copyright. The unabridged version of the thesis can be found in the Lancester Library, Coventry University.

Figure B.5 'Dataset' page and 'Download' link

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Figure B.6 'Contact' page

Appendix C Research Ethics Approval

P19095

P19095

Sar

Sarni Ral