UNIVERSITI PUTRA MALAYSIA

COMPUTER-AIDED DIAGNOSIS OF DIABETIC PATIENTS BASED ON COLOR FUNDUS IMAGES USING MACHINE LEARNING TECHNIQUES

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COMPUTER-AIDED DIAGNOSIS OF DIABETIC PATIENTS BASED ON COLOR FUNDUS IMAGES USING MACHINE LEARNING TECHNIQUES

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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COMPUTER-AIDED DIAGNOSIS OF DIABETIC PATIENTS BASED ON COLOR FUNDUS IMAGES USING MACHINE LEARNING TECHNIQUES

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Chair: Abd Rahman Ramli, PhD
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Diabetic retinopathy (DR) and diabetic macular edema (DME) are regarded as the most common complications of diabetes that, if not treated accordingly, could result in blindness. Early diagnosis and treatment planning can be considered as an essential step in preventing the vision loss, but the large and growing number of diabetic patients coupled with difficulties in screening a high number of patients makes early diagnosis difficult. Additionally, most of the time, a non-trivial inter- and intra-observer variability can be observed, depending on the point in time or the level of experience, different persons or even the same person may outline the anatomical boundaries differently. Computer-assisted diagnosis can be used for checking the retinal condition at different time intervals, providing a fast and reliable way of monitoring patient's condition during different time frames. However, most of the proposed methods do not contain any grading capabilities and are mostly designed for screening purposes.

The proposed computer-assisted diagnosis approach starts with the segmentation of the blood vessels. Then, optic disk and macula regions are located and segmented. Removing vessels, optic disk and macula regions increases accuracy of microaneurysm and exudate segmentation. Finally, retinal images are classified and graded using an AdaBoost classification method based on features extracted utilizing first, second and higher order image features selected by a minimal-redundancy maximal-relevance feature selection approach. Being brighter than the surrounding tissue, optic disk (OD) causes rapid variations in image intensity. This variation can be used for locating the OD region. In our study, OD is located using a variance based approach with OD outline segmented using circular Hough transform. By leveraging the location and the diameter of segmented OD, it is possible to locate the macula region as its position is relatively constant compared to OD. In this study, an exudate segmentation approach based on Kirsch's Edges method is used with the microaneurysms being segmented using mathematical morphology and thresholding approaches.

In this thesis, for each retina image, a feature vector with a fixed size is generated regardless of the position or the number of exudates and microaneurysms, which might not be properly segmented and used in an AdaBoost classifier for screening and grading images with possible signs of diabetic retinopathy and diabetic macular edema. The accuracy of the proposed diabetic grading approaches were comparable to other state of the art methods with an average accuracy of 0.791 and 0.974 in publicly accessible MESSIDOR dataset, respectively. By utilizing computer vision and machine learning concepts, it is possible to increase the DME detection rate considerably as CAD can reduce the workload of the ophthalmologists.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

DIAGNOSIS BERBANTU KOMPUTER BAGI PESAKIT DIABETIK BERDASARKAN WARNA IMEJ FUNDUS MENGGUNAKAN TEKNIK PEMBELAJARAN MESIN

Oleh

NOGOL MEMARI

Januari 2019

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Diabetik retinopati (DR) dan edema makular diabetes (DME) dianggap sebagai komplikasi diabetes yang paling biasa yang, jika tidak dirawat dengan sewajarnya, boleh menyebabkan kebutaan. Diagnosis awal dan perancangan rawatan boleh dianggap sebagai langkah penting dalam mencegah kehilangan penglihatan, tetapi jumlah pesakit diabetes yang besar dan berkembang ditambah dengan kesulitan dalam menyaring sejumlah besar pesakit membuat diagnosis awal sukar. Di samping itu, kebanyakan masa, ketidaktentuan antara dan bukan pengamatan yang tidak remeh dapat dipatuhi, bergantung pada titik waktu atau tahap pengalaman, orang yang berlainan atau orang yang sama dapat menggariskan batas-batas anatomi secara berbeza. Diagnosis dibantu komputer boleh digunakan untuk memeriksa keadaan retina pada selang waktu yang berlainan, menyediakan cara pemantauan pesakit yang cepat dan boleh dipercayai semasa bingkai masa yang berlainan. Walau bagaimanapun, kebanyakan kaedah yang dicadangkan tidak mengandungi keupayaan penggredan dan kebanyakannya direka untuk tujuan pemeriksaan.

Pendekatan diagnosis yang dibantu komputer yang dicadangkan bermula dengan segmen saluran darah. Kemudian, cakera optik dan kawasan makula terletak dan dibahagikan. Mengeluarkan kapal, cakera optik dan kawasan makula meningkatkan ketepatan mikroaneurisma dan pembahagian exudate. Akhir sekali, imej retina diklasifikasikan dan digredkan menggunakan kaedah klasifikasi AdaBoost berdasarkan ciri-ciri yang diekstrak dengan menggunakan ciri imej pesanan pertama, kedua dan lebih tinggi yang dipilih oleh pendekatan pemilihan ciri maksimal-relevansi minimum yang redundansi. Menjadi lebih cerah dari tisu sekitarnya, cakera optik (OD) menyebabkan perubahan pesat dalam keamatan imej. Variasi ini boleh digunakan untuk mencari kawasan OD. Dalam tesis, OD terletak dengan menggunakan pendekatan berasaskan varians dengan garis besar OD yang dibahagikan menggunakan transformasi Hough pekeliling. Dengan memanfaatkan lokasi dan diameter OD yang tersegmentasi, mungkin untuk mencari rantau makula kerana kedudukannya agak tetap

berbanding dengan OD. Dalam kajian ini, pendekatan segmentasi eksudat berdasarkan kaedah Kirsch's Edges digunakan dengan microaneurysms yang dibahagikan dengan menggunakan morfologi matematik dan pendekatan ambang.

Dalam tesis ini, bagi setiap imej retina, ciri vektor dengan saiz tetap dijana tanpa mengira kedudukan atau bilangan exudates dan microaneurysms, yang mungkin tidak dibahagikan dengan betul dan digunakan dalam pengelas AdaBoost untuk pemeriksaan dan penggredan imej dengan tanda-tanda yang mungkin daripada retinopati diabetik dan edema makular diabetes. Ketepatan pendekatan diabetes yang dicadangkan adalah setanding dengan kaedah seni yang lain dengan ketepatan purata 0.791 dan 0.974 dalam dataset MESSIDOR yang boleh diakses secara umum. Dengan menggunakan visi komputer dan konsep pembelajaran mesin, adalah mungkin untuk meningkatkan kadar pengesanan DME dengan ketara kerana CAD boleh mengurangkan beban kerja pakar mata.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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This is to confirm that:

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LIST OF ABBREVIATIONS

ANN	Artificial neural networks
BDA	British diabetic association
CAD	Computer Aided Diagnosis
CCWT	Complex continuous wavelet transform
CNN	Convolutional neural network
CRF	Conditional random fields
CSME	Clinically significant macular edema
CWS	Cotton wool spot
DM	Diabetes mellitus
DME	Diabetic macular edema
DoG	Difference of Gaussians
DR	Diabetic retinopathy
DWT	Discrete Wavelet Transform
EHD	Edge Histogram Descriptor
ELM	Extreme learning machine
FA	Fluorescein Angiography
FAR	Foveal Avascular Region
FCM	Fuzzy c-means
FLDA	Fisher's Linear Discriminant Analysis
FM	Frequency Modulation
FN	False negative
FOV	Field-of-view
FP	False positive
GDD	Gaussian Data Description
GLCM	Gray level co-occurrence matrix
GMM	Gaussian mixture model
HOS	Higher Order Spectra
HSI	Hue Saturation Intensity
HSL	Hue, Saturation, Luminance
LUT	Look-up table
MAP	Maximum a posteriori
MCA	Morphological component analysis
ME	Macular edema
MFR	Matched filter response
MP	Max Probability
MWT	Morlet Wavelet Transform
NN	Neural network
NPDR	Non-Proliferative Diabetic Retinopathy
NPV	Negative predictive value
NTSC	National Television Systems Committee
OCT	Optical Coherence Tomography
OD	Optic disk
ODD	Optic disc diameter
OOD	Of the optic disk diameter
PCA	Principal Component analysis
PDR	Proliferative Diabetic Retinopathy
PPV	Positive predictive value
PSO	Particle swarm optimization

RBF	Radial basis kernel functions
RF	Random Forest
RGB	Red, Green and Blue
ROC	Receiver operating characteristic
RRGT	Recursive Region-Growing Technique
RTA	Retinal thickness analyzer
SLIC	Simple linear iterative clustering
SLO	Scanning Laser Ophthalmoscope
SVM	Support vector machines

CHAPTER 1

INTRODUCTION

Diabetes is one of the leading causes of new cases of blindness worldwide. It is responsible for nearly 10% of the healthcare cost and the number of people suffering from diabetes estimated to be over 350 million by 2030 (World Diabetes, 2018). Diabetes is also considered as the 5th deadliest disease in the United States (Taylor and Batey, 2012). Approximately, half of the patients with diabetes are not aware of their disease. Therefore, the early diagnosis of diabetes plays a crucial role in management and treatment planning of patients. The increase in the number of patients with diabetes can be attributed to urbanization coupled with environmental and social factors such as an unhealthy diet, obesity and reduced physical activity (Sivaprasad et al., 2012).

Digital retinal imaging can be considered as a low-cost method of screening for diabetes and could be used in conjunction with computerized image processing techniques for automatic detection of signs of diabetes-related pathologies in retinal images. Diabetic Retinopathy (DR), often regarded as one of the most common complications of diabetes, can result in blindness if not treated accordingly as treatment of complications as a result of progressive and untreated DR is difficult (Kumar, 1998). Diabetic Macular Edema (DME), sometimes referred to as macular edema (ME), is a severe complication resulting from DR and could be considered as the most common cause of vision loss (Abràmoff et al., 2016). DME refers to the swelling of the retina in diabetic patients due to fluid leakage from small, dilated blood vessels. It is formed as the result of chronic damage due to an increased level of blood sugar within the center of the macula. The presence of clinically significant DME requires immediate medical intervention and laser treatment to prevent blindness (Nayak et al., 2008). Early diagnosis and treatment planning can be considered as an essential step in preventing the vision loss, but the increasing number of diabetic patients coupled with screening difficulties makes early diagnosis difficult. Imaging the vasculature network and anatomical structures in retinal images can be an effective tool for early detection of diabetes. As mentioned by Patton et al. (2006): “The retinal microvasculature is unique in that it is the only part of the human circulatory system that can be directly visualized non-invasively in vivo, readily photographed and subject to digital image analysis.” Direct ophthalmoscopy (manual inspection of retinal images by a specialist) is being challenged by computer-assisted diagnosis of retinal images. Direct ophthalmoscopy using retinal fundus images could be considered as an effective approach for diagnosing various retina-related diseases that can result in blindness such as macular degeneration and diabetic retinopathy. However, it is time consuming and the results cannot be easily reproduced. On the other hand, computer-assisted diagnosis of retinal fundus images has been shown to be as accurate as direct ophthalmoscopy and also faster and more reliable (Abràmoff et al., 2016).

1.1 Problem Statement

The human eye is responsible for vision and can be considered as one of the most important amongst the five human senses. Often, damaged retinal structures cannot be repaired. Majority of ocular diseases such as diabetic retinopathy and diabetic macular edema often show no early warning signs until the time that the disease has progressed and the treatment has become difficult. As a result, periodic retinal examinations for detecting early signs of ocular diseases such as changes in the blood vessel topology and presence of exudates are highly desired. However, manual segmentation of anatomical structures and grading of retinal disease by specialist ophthalmologists is a time-consuming process. Additionally, most of the time, a non-trivial inter- and intra-observer variability can be observed. Depending on the acquisition time or the level of experience, different persons or even the same person may outline the anatomical boundaries differently. Therefore, a robust and reliable automatic segmentation and computer aided analysis for supporting the ophthalmologist during diagnosis and/or treatment planning is needed.

Computer-assisted diagnosis of retinal images can be considered as an alternative to manual examination by ophthalmologists that can reduce the cost and complexity associated with grading and detecting diseases using retinal images. Computer-assisted diagnosis can be used for checking the retinal condition at different time intervals, providing a fast and reliable way of monitoring patient's condition during different time frames. CAD systems for use in DR and/or DME detection makes screenings possible for remote locations. In areas where it might be difficult for the population to be screened by medical professionals, CAD systems are used for screening a large population in a reasonable time frame (Liesenfeld et al., 2000). Recently, two large scale benchmark datasets designed for use in development of CAD systems capable of screening and grading of DR and DME has been proposed that makes it possible to design, test and compare different CAD systems for ensuring an adequate sensitivity and specificity of any proposed CAD system.

Automatic computer-aided screening of DR can be considered as an important factor that can reduce the percentage of untreated patients as it can provide reliable and automatic DR screening thus reducing the time, cost and the manual effort of mass screening (Fleming et al., 2010). While some studies focus mainly on sensitivity (recognition of patients having DR), the specificity (recognition of patients not having DR) of the screening system should also be considered in order to keep the CAD system as efficient as possible (Abràmoff et al., 2016). Additinally, as mentioned in (Sánchez et al., 2011), human grading of DR is highly subjective and depends on the examiner's experience. Hence, an automatic grading system that could reduce the inter-reader variability is needed. Moreover, screening by a CAD system can provide a competent alternative to analysis of fundus images by ophthalmologists in mass and/or remote screening scenarios. By excluding normal images, the time required to manually check the images is reduced as almost 70% of images in DR screening initiatives have no sign of DR (Roychowdhury et al., 2014; Dupas et al., 2010). However, in order to be able to exclude normal cases, algorithms must possess high specificity and high sensitivity, especially in moderate to severe cases (sight-threatening) of DR in order to avoid misdiagnosis of potentially sight-threatening retinopathy.

Nonetheless, ultimately, the purpose of using a computer-assisted diagnostic system should be to go beyond the binary classification of normal/abnormal images and to limit manual grading to images that have a certain degree of abnormality by providing the DR grades. This would mean that patients would only need to be referred to an ophthalmologist if they presented with moderate non-proliferative DR or worse, or patients with signs of DME. By utilizing computer vision and machine learning concepts, it is possible to increase the DME and DR detection rates considerably as CAD can reduce the workload of the ophthalmologists as confirmed by recent large-scale studies (Fleming et al., 2010; Giancardo et al., 2012, Roychowdhury et al., 2014, Sreejini and Govindan, 2013; Zaidi et al., 2013). However, most of these method do not contain any grading capabilities and are mostly designed for screening purposes. Although beneficial, computer based grading does not only reduce the workload of the ophthalmologists, it can also result in better prognosis by providing a second opinion on patient's condition.

1.2 Research Aim and Objectives

This study intends to develop an improved framework for segmentation of anatomical structures in the retina. Additionally, to develop computer-assisted diagnostic of retinal images with high accuracy by utilizing a different variety of image segmentation and machine learning (boosting) concepts. The objectives of the thesis are as follows:

i) To design an accurate retinal blood vessel, exudate and microaneurysm segmentation methods with using machine learning methods.
ii) To design an accurate computer-assisted diabetic retinopathy diagnosis and grading method.
iii) To design an accurate computer-assisted diabetic macular edema diagnosis and grading method.

1.3 Scope and Contribution of the Thesis

In this study, publicly accessible clinical datasets (Staal et al., 2004; Owen et al., 2009; Hoover et al., 2000; Decencière et al., 2014; Giancardo et al., 2012) designed to be used as a benchmark for different retinal vessel and computer-assisted diagnosis methods have been utilized. The proposed method was validated using all the images from available datasets and not subset of images was excluded. Furthermore, the vessel segmentation performance of the proposed method was validated using all the images from available datasets.

First, vessel segmentation can be considered as an important step toward automated retina analysis tools. The segmented vessels can be used for advance retina image analysis such as computing the vessel tortuosity and diameter, differentiating arteries and veins along with measuring the arteriovenous ratio. Moreover, segmented vessels are routinely used as features in retinal disease classification systems that can be used in the identification of several systematic diseases such as stroke, hypertension or diabetes, to name a few.

Then, while some DR detection approaches are based on the number of segmented red lesions (Bhaskaranand et al, 2015; Hansen et al, 2004) and some DME detection approaches are based on the number and location of exudates (Nayak et al, 2008), a combination of different statistical and anatomical features are used in this study that is not dependent on the number of segmented anatomical markers such as exudates. In this study, for each retina image, a feature vector with a fixed size is generated regardless of the position or the number of different lesions, which might or might not be properly segmented. Instead, the detected lesion candidates are described as a whole by analyzing the exudate and red lesion (microaneurysm) candidates. This approach makes it possible to test and train the AdaBoost based machine learning algorithm without requiring the ground truth at a lesion level as only the diagnosis for each particular image is required. The proposed method was implemented and tested utilizing MATLAB R2016a using Intel Core i5 CPU running at 2.67 GHz coupled with 4 gigabytes of RAM.

For screening cases, a yes/no decision is sufficient for referral to medical specialists as long as the system is able to detect any abnormalities in the retinal image, even if minimal. However, having a CAD approach capable of providing grades for DR and DME is highly desired as each grade have medically specific monitoring, treatment and response requirements.

1.4 Outline of the Thesis

The organization of the remaining chapter of the thesis is as follows:

Chapter Two acquaintances the reader with different imaging and machine learning concepts related to medical imaging. Then, different problems faced during vessel and different retinal structure segmentation and different approaches proposed for these segmentations are reviewed. Finally, the advantages and disadvantages of these approaches are discussed and conclusions derived from previous works are presented.

Chapter Three deals with the methodology of the developed framework and discusses the main ideas and approach relevant to the implementation of the different technique for the segmentation and classification of different structures inside the retina.

Chapter Four deals with the medical evaluation of the obtained vessel segmentation and highlights the performance of the developed CAD frameworks for DR and DME. The proposed CAD frameworks are compared with other methods in the literature, showing its performance along with its weaknesses. Chapter Five summarizes the proposed algorithm and discusses the obtained performance and possible future works.

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LIST OF PUBLICATIONS

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