DEVELOPMENT OF AN ENSEMBLE TRANSFER LEARNING-BASED CONVOLUTIONAL NEURAL NETWORKS MODEL FOR GRADING OF DIABETIC RETINOPATHY

BY

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A thesis submitted in fulfillment of the requirements for the degree of Master of Science (Computer and Information Engineering)

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JULY 2020

ABSTRACT

Diabetic Retinopathy (DR) is one of the diseases that infect people who suffer from diabetes. This chronic disease harms the patient retina and is considered one of the main causes of total blindness for people in the mid-age. Diagnosis of this disease is time-consuming and not accessible in some countries where the number of patients is very big comparing to the number of ophthalmologists. Therefore, designing and developing automated systems to grade DR is considered one of the recent research areas in the world of medical image applications. In this research, a complete pipeline for retinal fundus images processing and analysis was described, implemented and evaluated. This pipeline has three main stages: (i) image pre-processing, (ii) features extraction and (iii) classification. In the first stage, the image was pre-processed using different transformations techniques. In the second stage, the convolution neural network algorithm (CNN) was used. The concept of transfer learning and fine-tuning were advocated in this research. ResNet, DenseNet, and SqueezeNet were fine-tuned in order to implement the features extraction stage. For the classifier in the last stage, decision tree-based algorithms with the concept of ensemble learning were used where Random Forest, XGBoost and LightGBM were implemented and evaluated. Kaggle diabetic retinopathy dataset, a publicly available dataset, of retinal fundus image was used for training and testing. The problem of DR diagnosis was handled as a multi-class classification problem where there are five levels of the disease severity (0 – No DR, 1 – Mild, 2 – Moderate, 3 – Severe, 4 – Proliferative DR). The final model developed in this research used ResNet101 and DenseNet169 for features extraction, and it used the XGBoost for classification. It produced a very accurate performance with a quadratic weighted kappa score of 91.4% and an accuracy of 96.5%. This research proves that using CNN as a features-extractor algorithm is highly efficient since it produced representative features for the used images dataset. It shows that using the imbalanced dataset sampler is a very efficient solution to handle the issue of the imbalanced dataset. Also, it proves that ensemble learning algorithms are very promising algorithms to be used since they produced a very accurate model. The final model developed in this research could be used as the main unit for a computer-aided system (CAD) to be hosted online for DR diagnosis.

خلاصة البحث

اعتلال الشبكية السكري هو أحد الأمراض التي تصيب الأشخاص الذين يعانون من مرض السكري. يعتبر هذا المرض المزمن – والذي يضر بشبكية العين – أحد الأسباب الرئيسية للعمى التام الذي يصيب الأشخاص في منتصف العمر.
إن تشخيص هذا المرض يستغرق وقتاً طويلاً إضافة لكون عملية التشخيص غير متاحة في بعض البلدان نتيجة لعدد المرضى الكبير مقارنة بعدد أطباء العيون، لذلك يعد بناء وتطوير الأنظمة المؤتمتة المسؤولة عن كشف وتقييم مستوى المرض أحد مجالات البحث الحديثة في مجال تطبيقات الصور الطبية. في هذا البحث تم توصيف مسار كامل لمعالجة وتحليل صور قاع الشبكية إضافة لتطبيقه واختباره، يتألف هذا المسار من ثلاث مراحل أساسية ١) معالجة الصورة ٢) استخراج المميزات ٣) مرحلة التصنيف. يتم في المرحلة الأولى معالجة الصورة باستخدام تحويلات مختلفة. في المرحلة الثانية تم استخدام شبكة عصبونية من نوع CNN والتي تعد أحد أفضل الشبكات في مجال معالجة وتحليل الصور. حيث تم الاعتماد على مبدأي نقل التعلم (Transfer Learning) وإعادة الضبط (Fine Tuning). تم تطبيق مفهوم إعادة الضبط (Fine Tuning) على الشبكات العصبونية التالية ResNet, DenseNet, SqueezeNet وذلك من أجل استخراج المميزات. من أجل بناء المصنف في المرحلة الأخيرة تم الاعتماد على خوارزميات شجرة القرار مع تطبيق مبدأ تعلم المجموعة (ensemble learning) حيث تم تطبيق واختبار ثلاث خوارزميات بشكل أساسي وهي Random Forest, XGBoost, LightGBM. من أجل التدريب والاختبار تم الاعتماد على مجموعة بيانات اعتلال الشبكية السكري الموجودة على موقع Kaggle والتي تحوي مجموعة صور لقاع الشبكية. تم التعامل مع المشكلة المطروحة كمشكلة متعددة الأصناف حيث هناك خمس مستويات للمرض وهي ٠) سليم، ١) طفيف، ٢) متوسط، ٣) شديد، ٤) تكاثري. النموذج النهائي المعتمد في هذا البحث تم تطويره بالاعتماد على الشبكات العصبونية التالية ResNet101, DenseNet من أجل استخراج المميزات واستخدام خوارزمية XGBoost من أجل التصنيف وحقق نتائج دقيقة جداً، فبالنظر لمعيار quadratic weighted kappa حقق نتيجة ٩١,٤% إضافة للوصول لدقة مساوية لـ ٩٦,٥%. يثبت هذا البحث أن استخدام شبكات الـ CNN كخوارزمية لاستخراج المميزات له كفاءة عالية حيث ينتج ميزات دقيقة جدا في تمثيل الصورة وذلك من أجل مجموعة البيانات المستخدمة. كما يوضح أن استخدام خوارزمية الاعتيان غير المتوازن هو حل فعال للغاية عند التعامل مع مجموعة بيانات غير متوازنة. يثبت هذا البحث أيضا أن استخدام مبدأ تعلم المجموعة يعتبر واعد جداً في سياقات مشابهة بالنظر للنماذج الدقيقة التي ينتجها. إن النموذج النهائي الذي تم تطويره في هذا البحث يمكن استضافته عبر الانترنت واستخدامه كمحور رئيسي لأي نظام يعمل على كشف وتشخيص مرض اعتلال الشبكية السكري.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion; it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Science (Computer and Information Engineering)

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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ACKNOWLEDGMENTS

Firstly, it is my utmost pleasure to dedicate this work to my dear wife, Nazmeia Harah, who granted me the gift of her unwavering belief in my ability to accomplish this goal: thank you for your support and patience.

Secondly, I have to thank my parents for their love and support throughout my life. Thank you both for giving me the strength to reach for the stars and chase my dreams.

Also, I would like to thank Dr. Muhanad Hreh for providing me with information regarding diabetic retinopathy and answering any medically related questions. (Muhanad Hreh, M.D. Pikeville MedicalCenter, KY, USA).

I wish to express my appreciation and thanks to those who provided their time, effort and support for this project. To the members of my dissertation committee, thank you for sticking with me.

Finally, a special thanks to Professor Rashidah Funke Olanrewaju for her continuous support, encouragement and leadership, and for that, I will be forever grateful.

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LIST OF ABBREVIATIONS

AI	Artificial Intelligence
AUC	Area Under Curve
AMG	Age-related Macular Generation
ANN	Artificial Neural Network
CAD	Computer Aided Diagnosis
CNN	Convolutional Neural Network
DR	Diabetic Retinopathy
IDF	International Diabetes Federation
KNN	K Nearest Neighbors
LUV	LUV Color space

NPDR	Non-Proliferative Diabetic Retinopathy
PDR	Proliferative Diabetic Retinopathy
RGB	Red Green Blue
WP	Western Pacific
SVM	Support Vector Machine
PNN	Probabilistic Neural Network
HE	Histogram Equalization
CLAHE	Contrast Limited Adaptive Histogram Equalization
DT	Decision Tree
CART	Classification and Regression Trees
GOSS	Gradient-based One-Side Sampling
EFB	Exclusive Feature Blending
TP	True Positive
TN	True Negative
FP	False Positive
FN	False Negative

CHAPTER ONE

INTRODUCTION

١,١ OVERVIEW

Diabetes is a chronic disease causing the sugar (glucose) level in the blood to arrive at dangerously high levels. Glucose is vital to the body because it is an important source of energy for the cells that make up muscles and tissues. Meanwhile, insulin, a hormone that comes from the pancreas, is secreted into the bloodstream to burn the sugar in order to lower it in the blood. Insufficient production of insulin or an inability of the body to correctly use insulin causes diabetes. Mainly there are two types of this disease (insulin-dependent and non-insulin-dependent diabetes, or juvenile-onset and adult-onset diabetes respectively).

The number of people diagnosed to have diabetes increases over the last years. According to the International Diabetes Federation (IDF), Atlas 7th edition in 2015 more than 415 million people worldwide are affected by diabetes. Also, according to IDF Western Pacific (WP) Atlas 8th Edition in 2017, there are approximately 158.8 million adults in the age range 20-79 years were living with diabetes in the IDF WP region, representing 9.5% of the population. More than 54% of the cases are without diagnosis. Approximately two-thirds of the cases of adults with diabetes in the WP region live in urban areas. In Atlas 9th edition 2019, it is reported that 463 million adults are currently living with diabetes. In Malaysia, there were over 3.492.600 cases of diabetes in 2017, and the number increases according to the official website of IDF[١]

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[١] https://idf.org/our-network/regions-members/western-pacific/members/108-malaysia.html

Over time, diabetes could cause eye diseases which eventually lead to blindness. One of these diseases is Diabetic Retinopathy (DR), also known as diabetic eye disease. DR is considered the main cause of blindness in the mid-age. Early diagnosis and detection of DR help provide the required treatment which could prevent or at least delay blindness. Most guidelines advise to do annual screening for no DR or mild DR and repeat screening in 6 months for moderate DR. Screening for DR is a very important step to detect the effects of DR since DR most often has no early warning signs. In order to do screening, retinal fundus photography is conducted using special cameras. After that, a specialist ophthalmologist will diagnose the image and report the case.

In order to automate the process of DR detection, researchers have found that artificial intelligence (AI) is a very promising direction especially after the successful applications of Artificial Neural Networks (ANN) in different domains such as (Faust, Acharya U., Ng, Ng, & Suri, 2012) and (Litjens et al., 2017). Nowadays, the computer vision field is one of the main research fields benefiting from the great abilities of a special type of ANN which is known as Convolutional Neural Network (CNN). CNN is a class of deep feedforward ANN mainly used in analyzing images contents. The strength of CNN is its two main components where one component is for feature extraction, and the other one is for pattern recognition. These two components are trained together in order to achieve the required task, which means, there is no need for human intervention in order to choose and design features for recognition. Usually features extraction process is considered one of the hardest tasks in traditional machine learning projects and researches.

Due to the fact that the first part of CNN is responsible for features extraction, and usually, the low-level features between images are common, such as edges and textures, a pre-trained model for a different problem can be used to solve another problem by taking the first part of the CNN and retraining the classification part which will save time and require less computational resources. This is known as Transfer Learning. The performance of the system could be enhanced if transfer learning has been applied on multiple pre-trained CNNs, and the final output is generated according to the decisions of all these CNNs using Ensemble Learning algorithms. Harnessing the efficiency of ensemble learning algorithms and time-saving transfer learning concept with the existence of many huge pre-trained and ready to use CNNs will lead eventually to build a highly accurate and efficient system.

١ , ٢ DIABETIC RETINOPATHY

Diabetic Retinopathy is a disease infecting the retina of people who have diabetes. The retina is the layer at the back of the eye which mainly contains nerves. This part is responsible for capturing the image and sending this image back to the brain. DR is a dangerous disease that could lead in the worst case to the total blindness. DR disease evolves through time and mainly has two stages. In the first stage, which is called non-proliferative diabetic retinopathy (NPDR), the small blood vessels in the retina will be weaker and could cause tiny bulges called micro-aneurysms. Usually, these bulges appear a few years after the beginning of diabetes. After a while, these micro-aneurysms start to burst which causes small blood spots, known as hemorrhages, on the retina. Also, damaged blood vessels due to diabetes start leak fluid and protein on the retina; this is known as exudates (Gulshan et al., 2016) as shown in Figure 1.1.

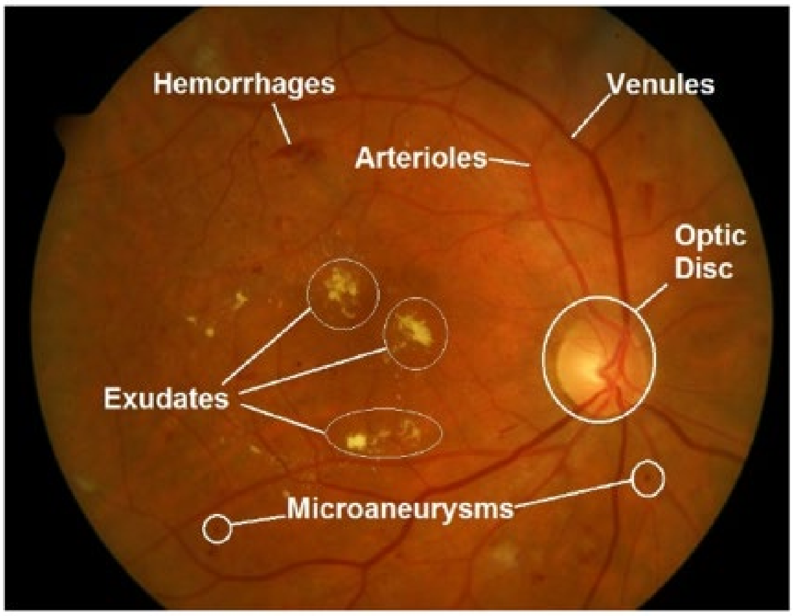

Figure 1. 1 NPDR Signs on the retina (Rakhlin, 2017)

In the second stage, which is called proliferative diabetic retinopathy (PDR), new abnormal weak blood vessels start to form and appear at the back of the eye due to reduced blood flow to the retina. These blood vessels burst and bleed. In the cases when bleeding happens for the first time, it will not be severe where it will leave some blood spots on the patient's visual field. These spots disappear after a few hours. However, if the disease is not treated, the bleeding could happen again after a few days or weeks with bigger blood spots which could blur the vision. In severe bleeding cases, the patient will be able to discriminate between dark and light areas only, and the spots need longer periods to disappear reaching to months or years in some cases(Gulshan et al., 2016).

Specialists classify the severity into four categories (1 - Mild DR, 2 - Moderate DR, 3 - Severe DR, 4 - Proliferative DR) (Pratt, Coenen, Broadbent, Harding, & Zheng, 2016) as shown in Figure1.2. Understanding the retinal fundus images is not an easy task, and it requires a specialist to check these images manually to check if there are any strange spots or signs of DR which makes the processing time consuming even for well-trained doctors. With this hard to be detected, quick to evolve, and slow to be diagnosed with a disease, the need for an automated system to detect this disease cannot be underestimated.

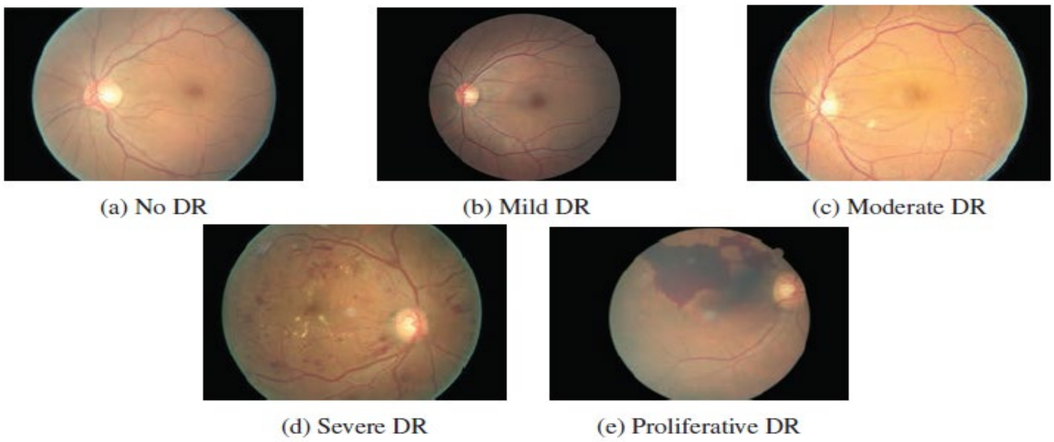

Figure 1. 2 DR Severity categories (Pratt et al., 2016)

١,٣PROBLEM STATEMENT

A regular diabetic retinopathy examination requires skilled and trained ophthalmologists to do the diagnosis from a retinal fundus image manually. This manual diagnosis puts a heavy workload on the ophthalmologists in which the process is time-consuming and requires focusing(Gargeya & Leng, 2017). When the number of cases to be diagnosed is small, this is not a problem. However, for a disease like diabetes, the number of patients is huge and is increasing daily. What worsens the problem is that this diagnosis should be done multiple times throughout the patient's lifetime(Gulshan et al., 2016). The problem becomes more complicated in countries that lack skilled ophthalmologists (Raman et al., 2019). Many researchers have acknowledged that most diabetes patients could be saved from DR through an early diagnosis (Raman et al., 2019). Therefore, building a computer-automated system to do the required diagnosis at an early stage is very important and necessary. Such a system will be very helpful, saves time, and mitigates the workloads of ophthalmologists.

Currently, most of the automated systems have been implemented using traditional machine learning algorithms which could succeed for one dataset but fail for another due to limitations of hand-crafted features (Bhatia, Arora, & Tomar, 2017) and (Asha & Karpagavalli, 2015), or been implemented using shallow convolution neural network due to lack of computational resources (Pratt et al., 2016). Although systems that have been implemented with the concept of transfer learning have achieved the most promising results (Wang, Fan, Reddy, & Wang, 2018), very few researches have been done on deep convolution neural networks using this concept. Also, there are a lot of huge pre-trained models, but very few models have appeared in the literature and there is no focus on this direction for DR detection. Still, those researches have handled the problem as a binary classification problem (healthy - unhealthy) (Hemanth, Deperlioglu, & Kose, 2019) whereas DR has two main stages and four levels of severity. Thus, DR detection by its nature is a multi-class classification problem. Although there are some researches have considered the problem as a multi-class classification problem, the problem of imbalanced dataset, which is a very common problem in deep learning medical applications, has not been handled (Pratt et al., 2016). Hence, this research is about an automated model focusing on solving the problem of DR detection and grading as a multi-class classification problem by combining the knowledge from multiple modern pre-trained models using ensemble learning algorithms for early diagnosis.

١,٤ RESEARCH OBJECTIVES

The main target of this research is to design and develop an ensemble transfer learning-based deep convolutional neural networks model for diabetic retinopathy detection and grading. Consequently, an efficient and accurate Computer-Aided Diagnosis (CAD) system for DR detection will be developed.

The specific objectives of the study are:

١- To propose the optimum image pre-processing techniques for the retinal fundus images.

٢- To identify the best pre-trained models for features extraction by applying transfer learning and fine-tuning on multiple pre-trained models.

٣- To develop and validated a new ensemble learning-based model considering the problem of imbalanced dataset to classify retinal fundus images into five levels of severity.

١,٥ RESEARCH METHODOLOGY

In this research, a model for DR detection and grading was designed and developed. In order to achieve this target, the research went through successive related steps.

١- First of all, a literature review of recent researches in the area was conducted. Also, a theoretical knowledge base about the dataset and the currently pre-trained models was built.

٢- In the second step, the dataset was downloaded, organized and pre-processed according to the research target.

٣- Next, using the pre-processed dataset, transfer learning and fine-tuning were applied on multiple pre-trained models to investigate the best models (Transfer learning part).

٤- A new model that combines the knowledge from the best models was designed, and implemented (Ensemble learning part).

٥- After implementing the final model, the full model was evaluated and compared with benchmarks in order to validate the performance of the model.

٦- Thesis writing was conducted through the research lifetime

The flowchart in Figure 1.3 summarized the proposed methodology.

١,٦ RESEARCH SCOPE

In this research, the problem of DR detection and grading was tackled as a multi-class classification problem. The problem was solved by designing and developing a new ensemble learning-based model using multiple pre-trained convolutional neural networks for feature extraction. Fine-tuning of CNNs or transfer learning was applied according to the resultant performance. Three pertained models were evaluated and tested in the scope of this research. These models were ResNet, DenseNet and SqueezeNet. The model works directly on coloured retinal fundus images. Therefore, anything related to segmentation algorithms is out of the scope of this research. Also, in order to train and test the model, the publicly available Kaggle dataset was used. Using datasets that do not contain images of the five grades of diabetic retinopathy is out the scope of this research. For the process of deep learning models training, Tesla K80 GPU of 12 GB RAM has been used. Any other equivalent or better GPU could be used. Therefore, hyper-parameters values were tuned taking into account the available memory size.