

Automatic Detection and Classification of Diabetic Retinopathy Stages in Retinal Image

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Abstract

This paper summarizes the different imaging techniques and methodologies used to perform classification of the different stages of a disease called diabetic retinopathy. In particular, it focuses on deep learning techniques to perform such detection in the fundus images of the patient's eye. Diabetic retinopathy is a progressive disease that causes the patient to lose eyesight if not diagnosed and treated at an early stage. Ophthalmologists usually diagnose the patient of this disease by screening the retinal fundus images to look for lesions. But the inaccuracy of such diagnosis together with the delay between diagnosis and treatment motivated researchers to automate this process of diagnosis. Using neural networks to train the system on a set of training images, it is possible to make systems that are more accurate and faster than human experts.

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Chapter 1

Introduction

1.1 General Overview

Visual perception is an integral part of human life. The eye is an organ that helps humans in this perception by allowing them to interact with the world. It involves sophisticated parts in the retinal region of the eye that reacts to the lighting condition to which it is exposed to. Such parts include the light sensitive rods and cones that send nervous impulses once light falls on it. These nervous impulses triggers the brain and causes it to detect the object that the person sees.

Although this method of sensing is very crucial to the humans, it can be easily impaired by various diseases, causing them to become blind in extreme cases. One such disease is Diabetic Retinopathy (DR) that is very common in diabetic patients and is one of the major reasons for such patients to lose their vision. It is also the fastest growing cause of blindness in the world. But it is possible to eliminate the risk of this disease if it is detected early and treated for accordingly.

The symptoms of this disease include growth of small legions or hemorrhages at its initial stages. Ophthalmologists can detect such symptoms of the disease by screening the fundus images of the eye. These are images of the retina taken through the pupil. Any hemorrhages or legions detected in the image ensures that the patient is positive of the disease. But detection of such lesions are difficult and often time consuming since they are very small and complex structures. Hence researchers are looking for ways to automate the detection procedure so that the ophthalmologists can concentrate on treating the disease rather than detecting.

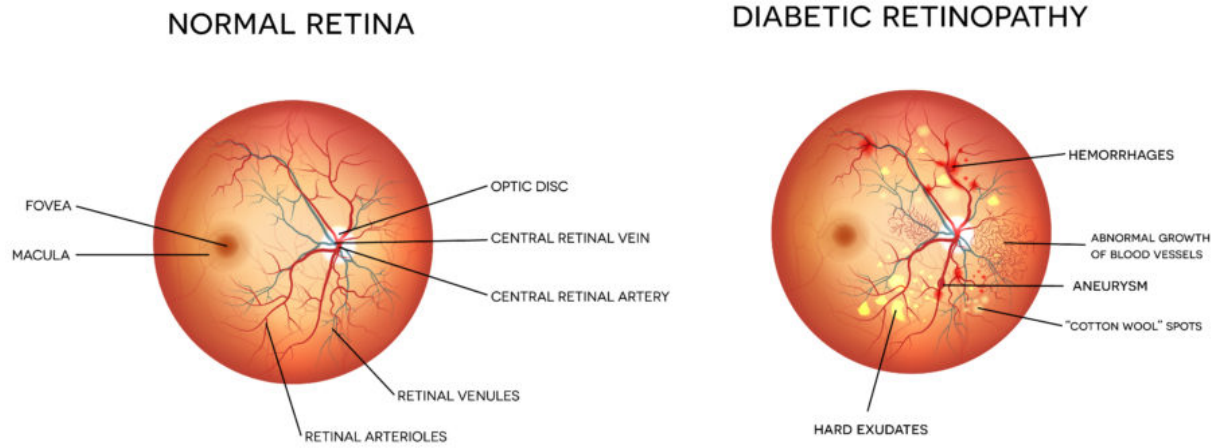


Figure 1.1: Normal versus diseased retina.

1.2 Motivation

The increasing number of diabetic patients and the influx in blindness among these patients caused by DR motivated us to work in this field. Also, the toll it takes on the ophthalmologists to detect the complex symptoms, motivated us to automate the system of detection so that they can concentrate more on treatment rather than detection. The delay between the detection and treatment procedure also drove us to work on this field because machines can detect the disease faster than humans.

1.3 Purpose of this report

This report initially elaborates on what the different stages of Diabetic Retinopathy are and what are the symptoms of such stages. It also includes the motivation that has driven us to work on this problem of automation. It then summarizes all the related works that have been done on detection of Diabetic Retinopathy using imaging techniques including works that have been done both with and without deep learning techniques. Lastly we conclude the report with our proposed methods and future works that can still be done in this field of research.

Chapter 2

Diabetic Retinopathy

2.1 Stages of Diabetic Retinopathy

Diabetic Retinopathy (DR) occurs when tiny blood vessels in the retina are damaged due to diabetes. These blood vessels leak blood or fluid forming lesions or hemorrhages that blur the vision of the patient. Each eye of a patient can be at different stages of the disease. But for the sake of simplicity, we broadly categorize the the disease into two categories:

- Non-proliferate diabetes retinopathy (NPDR)
- Proliferate diabetes retinopathy (PDR)

Non-proliferate PDR is the initial stage of DR where the biological abnormalities starts growing. Depending on the extent of the growth, the stages can be further categorized into mild and severe NPDR. If the disease still goes untreated, the final stage of the disease, Proliferate DR is achieved.

Once PDR is reached, new blood vessels start growing at a very fast rate. The tendency of the blood vessels to change and leak at the same time causes blindness or complete loss of vision. Hence the level of severity of the disease can be classified into 5 distinctive stages ranging from stage 0 to stage 4. Stage 0 is the safe state whereas stage 4 is the most severe stage that usually leads to blindness. The stages are:

- Stage 0: no DR
- Stage 1: mild DR
- Stage 2: moderate nonproliferative DR
- Stage 3: severe nonproliferative DR
- Stage 4: proliferative DR or Macular edema(ME)

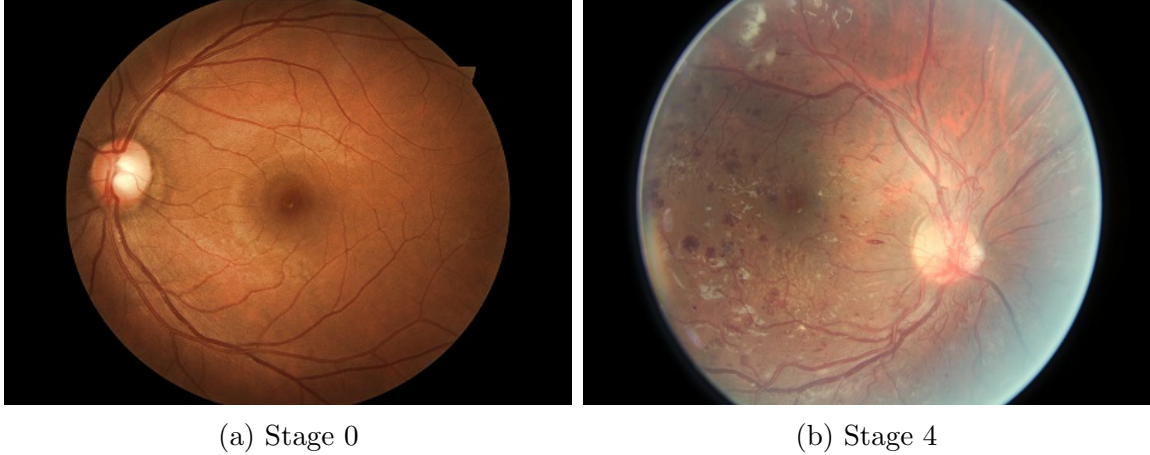


Figure 2.1: Safe state versus severe state.

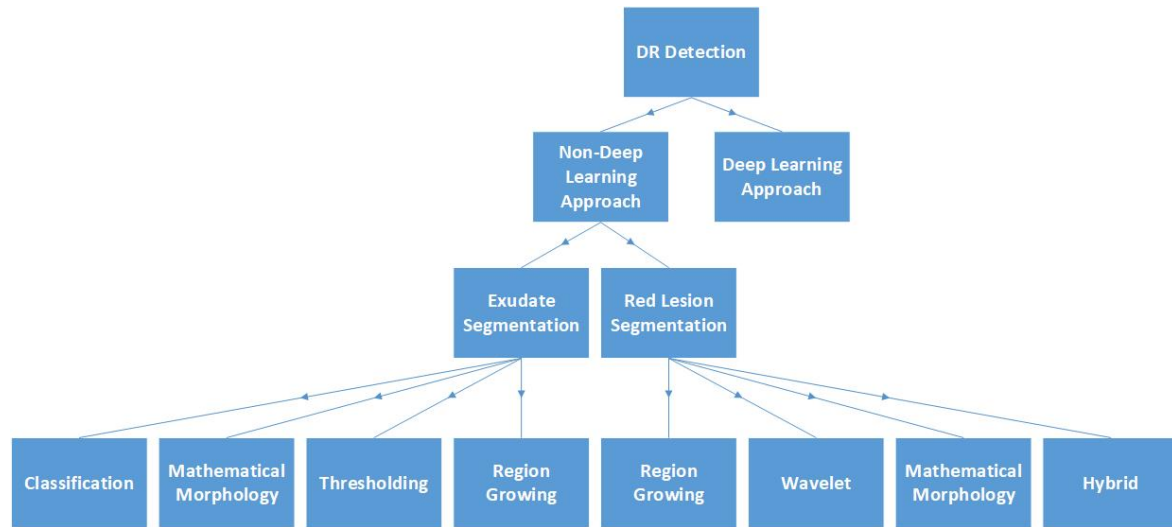
2.2 Image Dataset Available

In order to find a reliable model of neural network, we need a set of consistent high quality images that can be used to train and compare the performance of the networks. Some available datasets are DIARET DB0 [1], DIARET DB1 [2], MESSIDOR [3], and Kaggle [4]. Here we have listed the publicly available fundus image datasets that are available:

- Messidor-2 [3]: Dataset of 1748 labelled color fundus images of 874 subjects with diabetes. Images of both the eyes of the subject are present in the dataset.
- Kaggle Dataset [4]: Dataset of 35126 labeled color fundus images of diabetic subjects. The dataset contains images of both the eyes of the patients. But the number of images in different classes are unbalanced and the images are of different aspect ratio. So, they need to be pre-processed before training.

Chapter 3

Literature Review



3.1 Non Deep-Learning Methods

Most non-deep learning approaches consist of several steps. Preprocessing steps such as contrast enhancement are usually carried out initially to lessen image variation by normalizing the original retinal image. Afterwards, irrelevant anatomical components such as the optic disk and vessels are removed. Finally, only the remaining pathological features of DR are retained for subsequent classification.

Non-deep learning methods from 2015 or earlier can be grouped into two types: exudate

(EX) segmentation and red lesion (RL) segmentation.

3.1.1 Exudate Segmentation

EXs are lipoprotein intraretinal deposits due to vascular leakage. They appear in retinal images as yellowish lesions with well-defined edges. Their shape, size, brightness, and location vary among different patients. When clusters of EXs are located in the macular region, they are indicative of macular edema (ME), which is the main cause of visual loss in DR patients. For this reason, many researchers introduced the idea of a coordinate system based on the location of the fovea to determine DR grading. Different techniques have been proposed for EXs detection. They can be divided into four categories:

Region Growing Method

o **Automated detection of diabetic retinopathy on digital fundus images (2008) [5].**

- Authors: Sinthanayothin et al
- Purpose: develop an automated screening system to analyse digital colour retinal images for important features of non-proliferative diabetic retinopathy (NPDR).
- Method: High performance pre-processing of the colour images was performed. Previously described automated image analysis systems were used to detect major landmarks of the retinal image (optic disc, blood vessels and fovea). Recursive region growing segmentation algorithms combined with the use of a new technique, termed a Moat Operator, were used to automatically detect features of NPDR. These features included haemorrhages and microaneurysms (HMA), which were treated as one group, and hard exudates as another group.
- Features:
 - Hard exudates : identified as adjacent pixels with similar colour or grey level
 - HMA : sharpened using Moat Operator then identified by thresholding
- Classifier: Multilayer perceptron neural network to identify blood vessels
- Data: 112 digital fundus images of patients attending a DR screening service

- Results: sensitivity and specificity for exudate detection were 88.5% and 99.7%

Thresholding Method

o Detection of exudates in retinal images using a pure splitting technique (2010) [6].

- Authors: Jaafar et al
- Method: an adaptive thresholding based on a novel algorithm for pure splitting of the image is proposed. A coarse segmentation based on the calculation of a local variation for all image pixels is used to outline the boundaries of all candidates which have clear borders. A morphological operation is used to refine the adaptive thresholding results based on the coarse segmentation results
- Features:
 - Exudates : local variation for each pixel of exudate region with clear margins
 - o Non-exudates : discriminated using major axis length, minor axis length, area, solidity
- Data: 50 abnormal images from DIARETDB0 database screening service
- Results: 91.2% sensitivity, 99.3% specificity

o A novel automatic image processing algorithm for detection of hard exudates based on retinal image analysis (2008) [7].

- Authors: Sanchez et al
- Method: based on Fishers linear discriminant analysis and makes use of colour information to perform the classification of retinal exudates.
- Features:
 - Hard exudates : modified RGB model
 - Non-exudates : selecting pixels around optic disk depending on its area
- Classifier: Fishers linear discriminant (FLD)
- Data: 58 retinal images with variable colour, brightness, and quality

- Results: sensitivity of 88% using the lesion-based performance evaluation criterion, and accuracy of 100% (sensitivity of 100% and specificity of 100%) image-based classification

Mathematical Morphology Methods

o Exudate detection in color retinal images for mass screening of diabetic retinopathy (2014). [8]

- Authors: Zhang et al
- Purpose: automatically detect normal exams in a tele-ophthalmology network, thus reducing the burden on the readers
- Method: new preprocessing methods, which perform not only normalization and denoising tasks, but also detect reflections and artifacts in the image. A new candidates segmentation method, based on mathematical morphology. These candidates are characterized using classical features, but also novel contextual features. A random forest algorithm is used to detect the exudates among the candidates
- Features:
 - Contextual : distance between barycenter of candidate to nearest vessel, minimum distance of candidate to nearest vessel
 - Ultimate opening, a multi-scale morphological operator
 - Mean value of normalized saturation channel of each exudate candidate
- Classifier: Random forest method
- Data: A new clinical database, e-optha EX, containing precisely manually contoured exudates. It is very heterogeneous. It contains images gathered within the OPHDIAT telemedicine network for diabetic retinopathy screening
- Results: AUC between 0.93 and 0.95

o Automatic detection of diabetic retinopathy exudates from non-dilated retinal images using mathematical morphology methods (2008). [9]

- Authors: Sopharak et al

- Method: Preprocessing (RGB to HIS, median filter, contrast enhancement, optic disc elimination), exudates detection (closing, local variation, thresholding, morphological reconstruction)
- Features:
 - Exudate detection : size of structuring element in dilation, window size in local variation operator, threshold valued calculated using Otsu algorithm
 - Macular detection : Applying closing operator then thresholding
- Data: All digital retinal images were taken from patients with nondilated pupils taken at Thammasat University Hospital
- Results: Results: sensitivity and specificity are 80% and 99.5%

Classification Method

o **A computational-intelligence-based approach for detection of exudates in diabetic retinopathy images (2009).** [10]

- Authors: Osareh et al
- Objective: Automated identification of exudate pathologies in retinopathy images based on computational intelligence techniques.
- Method: The color retinal images are segmented using fuzzy c-means clustering following some preprocessing steps, i.e., color normalization and contrast enhancement. The entire segmented images establish a dataset of regions. To classify these segmented regions into exudates and nonexudates, a set of initial features such as color, size, edge strength, and texture are extracted. A genetic-based algorithm is used to rank the features and identify the subset that gives the best classification results. The selected feature vectors are then classified using a multilayer neural network classifier.
- Features:
 - Exudate discrimination : compactness of region, region size, region edge strength, mean Luv values inside and outside the region and Gabor filter response features
- Classifier: three-layer perceptron NN with 65 node input
- Data: large image dataset consisting of 300 manually labeled retinal images
- Results: 96.0% sensitivity, 94.6% specificity

o Neural network based detection of hard exudates in retinal images (2009).
[11]

- Authors: Garcia et al
- Method: an algorithm which includes a neural network (NN) classifier. Three NN classifiers were investigated: multilayer perceptron (MLP), radial basis function (RBF) and support vector machine (SVM)
- Features:
 - Exudates : mean RGB values inside and outside the region and their standard deviations, region size, compactness and edge strength
- Data: 117 images with variable colour, brightness, and quality. 50 of them (from DR patients) were used to train the NN classifiers and 67 (40 from DR patients and 27 from healthy retinas) to test
- Results: Using a lesion-based criterion, a mean sensitivity (SEI) of 88.14% and a mean positive predictive value (PPV1) of 80.72% for MLP. With RBF, SEI = 88.49% and PPV1 = 77.41%, while SEI = 87.61% and PPV1 = 83.51% using SVM

o Automated detection of exudates for diabetic retinopathy screening (2007).
[12]

- Authors: Fleming et al
- Method: Candidate exudates were detected using a multi-scale morphological process. Based on local properties, the likelihoods of a candidate being a member of classes exudate, drusen or background were determined. This leads to a likelihood of the image containing exudates which can be thresholded to create a binary decision
- Features:
 - Exudate candidate : normalized luminosity and its standard deviation, normalized boundary gradient, candidate area, distance from nearest MA detected, and standardized colour features
- Classifier: SVM having radial basis function kernel
- Data: 13 219 images of which 300 contained exudates
- Results: sensitivity 95.0% and specificity 84.6%

o Automated Detection and Differentiation of Drusen, Exudates, and Cotton-Wool Spots in Digital Color Fundus Photographs for Diabetic Retinopathy Diagnosis (2007). [13]

- Authors: Niemeijer et al
- Purpose: To describe and evaluate a machine learningbased, automated system to detect exudates and cotton-wool spots in digital color fundus photographs and differentiate them from drusen, for early diagnosis of diabetic retinopathy
- Method: : Each pixel was classified, resulting in a so-called lesion probability map that indicates the probability that a pixel is part of a bright lesion. Pixels with high probability were grouped into probable lesion pixel clusters. Based on cluster characteristics each probable lesion pixel cluster was assigned a probability indicating the likelihood that the pixel cluster was a true bright lesion. Each bright lesion cluster likely to be a bright lesion was classified as exudate, cotton-wool spot or drusen.
- Features:
 - True bright lesion detection : area, perimeter, compactness, length, width, mean gradient, mean of green channel pixels, mean CIE-LUV intensities, local pixel contrast, distance to closest red lesion
- Classifiers: k-NN and a linear discriminant analysis classifier
- Data: Three hundred retinal images from one eye of 300 patients with diabetes were selected from a diabetic retinopathy telediagnosis database (nonmydriatic camera, two-field photography): 100 with previously diagnosed bright lesions and 200 without
- Results: The system achieved an area under the receiver operating characteristic (ROC) curve of 0.95 and sensitivity/specificity pairs of 0.95/0.88 for the detection of bright lesions of any type

3.1.2 Red Lesion Segmentation

MAs are small saccular bulges in the walls of retinal capillary vessels. In color fundus images, MAs appear like round red dots with a diameter ranging from 10 to 100 μ m. MAs are difficult to distinguish from dot-HEMs, which are a little bigger. MAs are normally the first retinal lesions that appear in DR and their number has a direct relationship to DR severity. Several approaches have been proposed for MAs segmentation

through color image analysis. The techniques for RL detection can be also divided into four categories:

Region Growing Methods

o Automated microaneurysm detection using local contrast normalization and local vessel detection (2006). [14]

- Authors: Fleming et al
- Method: Various methods for contrast normalization are compared. Best results were obtained with a method that uses the watershed transform to derive a region that contains no vessels or other lesions. Dots within vessels are handled successfully using a local vessel detection technique
- Features: number of peaks in smoothed energy function, major axis length, eccentricity of the elliptical cross section of the paraboloid, depth of the candidate, energy at the boundary
- Classifier: k-NN with $k = 15$
- Data: images acquired from diabetic patients attending the Grampian Diabetes Retinal Screening Programme 1441 images were graded by a clinician for the presence of MAs
- Results: sensitivity 85.4% and specificity 83.1%

Mathematical Morphology Methods

o Automated microaneurysm detection method based on eigenvalue analysis using hessian matrix in retinal fundus images (2013). [15]

- Authors: Inoue et al
- Method: After image preprocessing, the MA candidate regions were detected by eigenvalue analysis using the Hessian matrix in green-channelled retinal fundus images. Then, 126 features were calculated for each candidate region. By a threshold operation based on feature analysis, false positive candidates were removed. The candidate regions were then classified either as MA or false positive using artificial neural networks (ANN) based on principal component analysis

(PCA). The 126 features were reduced to 25 components by PCA, and were then inputted to ANN

- Features: based on pixel value, shape, texture analysis, reduced using principal component analysis (PCA)
- Classifier: Classifier: artificial neural network (ANN)
- Data: 25 retinal images from the retinopathy online challenge (ROC) database
- Results: true positive rate was 73

o Automated detection of red lesions from digital colour fundus photographs (2011). [16]

- Authors: Jaafar et al
- Method: After pre-processing, a morphological technique was used to segment red lesion candidates from the background and other retinal structures. Then a rule-based classifier was used to discriminate actual red lesions from artifacts. A novel method for blood vessel detection is also proposed to refine the detection of red lesions
- Features: aspect ratio, area, perimeter, circularity, eccentricity, mean intensity, inner standard deviation
- Classifier: Rule-based classifier
- Data: standardised test set of 219 images
- Results: sensitivity of 89.7% and a specificity of 98.6% (at lesion level)

o Detection of microaneurysms using multi-scale correlation coefficients (2010). [17]

- Authors: Zhang et al
- Method: a new approach based on multi-scale correlation filtering (MSCF) and dynamic thresholding is developed. This consists of two levels, microaneurysm candidate detection (coarse level) and true microaneurysm classification (fine level)
- Features: area, perimeter, aspect ratio, circularity of the candidate, total, average and normalized intensities, compactness

- Classifier: Discrimination table
- Data: ROC (retinopathy on-line challenge) and DIARETDB1 (standard diabetic retinopathy database)
- Results: 2nd rank in ROC competition

o Automatic detection of microaneurysms in color fundus images (2007). [18]

- Authors: Walter et al
- Method: The first step consists in image enhancement, shade correction and image normalization of the green channel. The second step aims at detecting candidates, i.e. all patterns possibly corresponding to MA, which is achieved by diameter closing and an automatic threshold scheme. Then, features are extracted, which are used in the last step to automatically classify candidates into real MA and other objects; the classification relies on kernel density estimation with variable bandwidth
- Features: no. of pixels in region, circularity, mean and maximal values of top-hat, dynamic (a classical morphological contrast measure), outer and inner grey level mean and standard deviation, grey level contrast, colour contrast
- Classifier: KNN
- Data: 21 annotated images Grampian Diabetes Retinal Screening Programme 1441 images were graded by a clinician for the presence of MAs
- Results: sensitivity was 88.5% at an average number of 2.13 false positives per image

Wavelet-Based Method

o Optimal wavelet transform for the detection of microaneurysms in retina photographs (2008). [19]

- Authors: Quelled et al
- Method: MAs are detected by locally matching a lesion template in subbands of wavelet transformed images. To improve the method performance, the best adapted wavelet within the lifting scheme framework is used. The optimization process is based on a genetic algorithm followed by Powells direction set descent

- Data: 120 retinal images analyzed by an expert
- Results: sensitivity of 89.62%, positive predictive value of 89.50%

Hybrid Methods

o Retinal Microaneurysm Detection Through Local Rotating Cross-Section Profile Analysis (2013). [20]

- Authors: Lazar et al
- Method: MA detection through the analysis of directional cross-section profiles centered on the local maximum pixels of the preprocessed image. Peak detection is applied on each profile, and a set of attributes regarding the size, height, and shape of the peak are calculated subsequently. The statistical measures of these attribute values as the orientation of the cross-section changes constitute the feature set that is used in a naive Bayes classification to exclude spurious candidates. A formula for the final score of the remaining candidates is given, which can be thresholded further for a binary output
- Features: increasing and decreasing ramp height, ramp slope, top and peak width, peak height
- Classifier: Naive Bayes classifier
- Data: The ROC publicly available dataset consisting of 50 training and 50 test images
- Results: overall score of 0.423, ranked 2nd in ROC competition

o Assessment of four neural network based classifiers to automatically detect red lesions in retinal images (2010). [21]

- Authors: Garcia et al
- Objective: detect red lesions (RLs), like haemorrhages and microaneurysms
- Method: extracted a set of colour and shape features from image regions and performed feature selection using logistic regression. Four neural network (NN) based classifiers were subsequently used to obtain the final segmentation of RLs: multilayer perceptron (MLP), radial basis function (RBF), support vector machine (SVM) and a combination of these three NNs using a majority voting (MV) schema

- Features: Region size, mean and standard deviation of RGB values in and around the region, compactness, edge strength, homogeneity, colour difference, circularity, eccentricity, aspect ratio
- Classifiers: MLP, RBF, SVM
- Data: 115 images divided into a training set of 50 images (with RLs) and a test set of 65 images (40 with RLs and 25 without RLs)
- Results: best results were obtained for RBF. Using a lesion-based criterion, a mean sensitivity of 86.01% and a mean positive predictive value of 51.99% were obtained. With an image-based criterion, a mean sensitivity of 100%, mean specificity of 56.00%

o Mixture model-based clustering and logistic regression for automatic detection of microaneurysms in retinal images (2009). [22]

- Authors: Sanchez et al
- Method: a statistical approach based on mixture model-based clustering and logistic regression. The innovative segmentation approach based on a statistical mixture model based clustering allows a robust separation of the foreground and background scenes and, specifically, a segmentation of MAS in a totally unsupervised manner
- Features: based on shape, colour, brightness, contrast
- Classifier: logistic regression classifier
- Data: public database proposed by the Retinal Online Challenge
- Results: overall score in the ROC competition of 0.332404

o Automated microaneurysm detection method based on double-ring filter and feature analysis in retinal fundus images (2009). [23]

- Authors: Mizutani et al
- Method: After image preprocessing, candidate regions for microaneurysms were detected using a double-ring filter. Any potential false positives located in the regions corresponding to blood vessels were removed by automatic extraction of blood vessels from the images. Twelve image features were determined, and the

candidate lesions were classified into microaneurysms or false positives using the rule-based method and an artificial neural network

- Features: area, circularity, length to width ratio, mean value of red, green and blue bits, contrast
- Classifier: rule-based method and a three-layered feed forward ANN with back propagation algorithm
- Data: Retinopathy Online Challenge (ROC) database (50 training cases, 50 test cases)
- Results: sensitivity for detecting microaneurysms was 65% at 27 false positives per image

o Automatic detection of red lesions in digital color fundus photographs (2005). [24]

- Authors: Niemeijer et al
- Method: a new red lesion candidate detection system based on pixel classification. Using this technique, vasculature and red lesions are separated from the background of the image. After removal of the connected vasculature the remaining objects are considered possible red lesions. An extensive number of new features are added to those proposed by SpencerFrame. The detected candidate objects are classified using all features and a k-nearest neighbor classifier
- Features: area, perimeter, aspect ratio, circularity, total, mean and normalized intensities in green plane and shade corrected image, compactness, mean and standard deviation of filter outputs
- Classifier: kNN, linear discriminant, quadratic discriminant
- Data: 100 images and was used to train and test composed of data taken from a screening program.
- Results: sensitivity of 100% at a specificity of 87%

3.2 Deep Learning Methods

Feature engineering, involves computing explicit features specified by experts, resulting in algorithms designed to detect specific lesions or predicting the presence of any level

of diabetic retinopathy.⁵ Deep learning⁶ is a machine learning technique that avoids such engineering by learning the most predictive features directly from the images given a large data set of labeled examples. This technique uses an optimization algorithm called back-propagation to indicate how a machine should change its internal parameters to best predict the desired output of an image. Some of the papers using deep learning algorithms to create models are given in the following section.

3.2.1 Convolutional Neural Network

A convolutional neural network (CNN) is a class of deep, feed-forward artificial neural networks. CNNs use a variation of multilayer perceptrons via backpropagation designed to require minimal preprocessing. CNNs use relatively little pre-processing compared to other image classification algorithms. This means that the network learns the filters that in traditional algorithms were hand-engineered. This independence from prior knowledge and human effort in feature design is a major advantage.

Segmentation Using CNN

o Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs (2016). [25]

- Authors: Varun Gulshan et al
- Objective: To apply deep learning to create an algorithm for automated detection of diabetic retinopathy and diabetic macular edema in retinal fundus photographs.
- Method: CNN was implemented using Inception-v3 architecture proposed by Szegedy et al. The optimization algorithm used to train the network weights was a distributed stochastic gradient descent implementation by Dean et al.¹⁶ To speed up the training, batch normalization⁷ as well as preinitialization using weights from the same network trained to classify objects in the ImageNet data set¹⁷ were used. An ensemble¹⁹ of 10 networks trained on the same data was used, and the final prediction was computed by a linear average over the predictions of the ensemble.
- Data: The EyePACS-1 data set consisted of 9963 images and Messidor-2 data set had 1748 images

- Result: The performance of the algorithm at the high-sensitivity and high-specificity operating points are:
 - High-sensitivity operating point: specificity was 84.0% and sensitivity was 96.7%.
 - High-specificity operating point: specificity was 93.8% and sensitivity was 90.7%
 - The area under the receiver operating characteristic curve was 97.4%

o Improved Automated Detection of Diabetic Retinopathy on a Publicly Available Dataset Through Integration of Deep Learning (2016). [26]

- Authors: Michael David Abramoff et al
- Objective: To compare performance of a deep-learning enhanced algorithm for automated detection of diabetic retinopathy.
- Method: A hybrid device applies a set of CNN-based detectors to each of the images in the exam. These detectors are trained and optimized to detect normal retinal anatomy, such as optic disc and fovea, as well as the lesions characteristic for DR, such as hemorrhages, exudates, and neovascularization. They are inspired by Alexnet23 and the Oxford Visual Geometry Group26 network architectures. The analysis software provides four types of outputs:
 - Negative: implying no or only mild DR present
 - rDR: implying rDR is present
 - vtDR: implying vtDR is present
 - Low exam quality: implying either protocol errors or low quality of the individual images.

If the index is above or equal to the vtDR threshold, a positive output for vtDR is returned. If the vtDR index is below this threshold, the rDR index is thresholded. If the rDR index is above or equal to this latter threshold a positive output for rDR is returned. If it is below the latter threshold an output of negative is returned. The device was never trained on any of the Messidor-2 images.

- Data: 10,000 to 1,250,000 unique samples, depending on the lesion to be detected are used for training. Messidor-2 data consisting of 1748 images is used for validation.
- Result: The device with CNN based detectors performed pretty good with results of:

- vtDR: 100% sensitivity, 91% specificity and 0.989 AUC.
- rDR: 96.8% sensitivity and 87.0% specificity
- The area under the receiver operating characteristic curve was 97.4%

o Fast convolutional neural network training using selective data sampling: Application to hemorrhage detection in color fundus images (2016). [27]

- Authors: van Grinsven et al
- Objective: a method to improve and speed-up the CNN training for medical image analysis tasks by dynamically selecting misclassified negative samples during training
- Method: A dynamic CNN training strategy where informative normal samples are dynamically selected at each training epoch from a large pool of medical images. A dynamic weight is assigned to each pixel in the negative training pool indicating its informativeness level. After each CNN training epoch, the weight of each negative training pixel is updated. This process is repeated until a stopping criterion is reached. The final trained CNN is used to classify each pixel in the test images, resulting in a pixel probability map for each test image
- Network details: The CNN architecture used in this study consists of five convolutional layers followed by rectified linear units (ReLUs) and spatial max-pooling. The final layers of the network consist of a fully connected layer and a final softmax classification layer.
- Data: Kaggle and Messidor databases
- Result: A decreased training time from 170 epochs to 60 epochs with an increased performance on par with two human experts was achieved with areas under the receiver operating characteristics curve of 0.894 and 0.972 on two data sets. The SeS CNN statistically outperformed the NSeS CNN on an independent test set

o Convolutional Neural Networks for Diabetic Retinopathy (2016). [28]

- Authors: Pratt et al
- Objective: A network with CNN architecture and data augmentation which can identify the intricate features involved in the classification task such as micro-aneurysms, exudate and haemorrhages on the retina and consequently provide a diagnosis automatically and without user input

- Method: Preprocessing tasks such as colour normalization and resizing were performed. The network was trained using stochastic gradient descent with Nesterov momentum. Afterwards, real-time data augmentation was used throughout training to improve the localisation ability of the network
- Network details: The network starts with convolution blocks with activation and then batch normalisation after each convolution layer. As the number of feature maps increases they move to one batch normalisation per block. All maxpooling is performed with kernel size 3x3 and 2x2 strides. After the final convolutional block the network is flattened to one dimension. To avoid overfitting they used weighted class weights relative to the amount of images in each class. Likewise, they performed dropout on dense layers, to reduce overfitting, until they reached the dense five node classification layer which uses a softmax activation function to predict our classification. The leaky rectified linear unit¹³ activation function was used, applied with a value of 0.01, to stop over reliance on certain nodes in the network. Similarly, in the convolution layers, L2 regularisation was used for weight and biases. The network was also initialized with Gaussian initialisation to reduce initial training time. The loss function used to optimise was the widely used categorical cross-entropy function.
- Data: Kaggle databases
- Result: a sensitivity of 95% and an accuracy of 75% on 5,000 validation images

o Improved Microaneurysm Detection using Deep Neural Networks (2016). [29]

- Authors: Haloi et al
- Objective: a novel microaneurysm (MA) detection for early diabetic retinopathy screening using color fundus images
- Method: Each pixel of the image is classified as either MA or non-MA using a deep neural network with dropout training procedure using maxout activation function. No preprocessing step or manual feature extraction is required
- Network details: three convolutional layers each followed by a max-pooling layer and one fully connected layer. And a softmax layer on the top of the network with two neurons for MA and non-MA probability values
- Data: Retinopathy Online Challenge (ROC) and Diaretdb1v2 database
- Result: accuracy of 95% with sensitivity and specificity of 97% and 94% respectively on Messidor dataset

o Automated Identification of Diabetic Retinopathy Using Deep Learning (2017). [30]

- Authors: Gargeya et al
- Objective: to develop a data-driven deep learning algorithm to automate DR screening
- Network details: convolutional parameter layers learn iteratively filters that transform input images into hierarchical feature maps, learning discriminative features at varying spatial levels without the need for manually tuned parameters. each convolutional layer used batch normalization and the ReLU nonlinearity function to ensure smooth training and prevent overfitting, while using 2-class categorical cross-entropy loss for class discrimination
- Data: Messidor 2 and E-Opha databases
- Result: a 0.94 and 0.95 AUC score

Chapter 4

Implementation and Future Work

4.1 Implementation

Two implementations of diabetic retinopathy classification using CNN was attempted on a laptop computer having Core i7 2.6 GHz processor, 16 GB RAM and GTX 960M graphics card. These implementations were based on methods used by participants of Kaggle DR Classification Competition. The code was implemented using python programming language on ubuntu operating system. Library functions such as OpenCV, Theano, Lasagna and Tensorflow were used. Although the preprocessing scripts ran successfully in our setup, the network scripts could not be implemented since our system was not powerful enough to handle such large amount of computation. We used Kaggle DR database for these implementations.

4.2 Future Works

- Separation of training and validation datasets could be done before and after the augmentation to see how it performs.
- Use different ensemble methods to merge the network formed by CNN to see which performs better.
- Use the combination of layers in a neural network that gives a higher amount of accuracy for the dataset being used in the minimum amount of time and complexity.

- Use different preprocessing steps that increase the accuracy of the model such as:
 - Enhancement on images might enhance dirt on the lens making images of level 0 appear as level 4. So we need to compensate for this problem.
 - Images could be of different resolution. Enlarging all images to one common resolution might result in details to be lost. So we need to find optimum resolution for which the best accuracy is achieved.
 - There can be an unbalanced number of images in different classes. So we need to ensure consistency in the preprocessing step without overfitting.

Chapter 5

Conclusion

As discussed in this report, many work related to this field have already been using deep learning and feature based learning. But still, there is a scope to further enhance the techniques to improve efficiency and the complexity of the algorithms. Further research is necessary to determine the feasibility of applying this algorithm in the clinical setting and to determine whether use of the algorithm could lead to improved care and outcomes compared with current ophthalmologic assessment. And it is also very important that we address this problem at hand fast since the predicted numbers of people being infected by this disease are increasing everyday.

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