Identifying Signs of Diabetic Retinopathy Using Deep Learning

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I would like to bla bla

Declaration

I hereby declare...

Acknowledgements

And I would like to acknowledge....

Abstract

Diabetic Retinopathy is a visual impairment disease as a result of diabetes mellitus. Visual impairment caused by diabetic retinopathy(DR) can be cured if detected in earlier stage of DR in patients. In this work, we try to automatically detect signs of DR by using deep neural networks. For this purpose, we train deep neural network by using one of the widely used publicly available datasets and test with other public datasets. Experimental results show that deep learning techniques can be promising in the task of automatic detection of DR.

WILL BE EXTENDED

Contents

Chapter 1

Introduction

In this chapter, diabetic retinopathy and diagnosing diabetic retinopathy is discussed. The chapter contains the potential benefits of automated detection of diabetic retinopathy and eye fundus images. (Bu kisim degisecek - research question vs ekle)

1.1 Diabetic Retinopathy

1.1.1 Structure of Eye

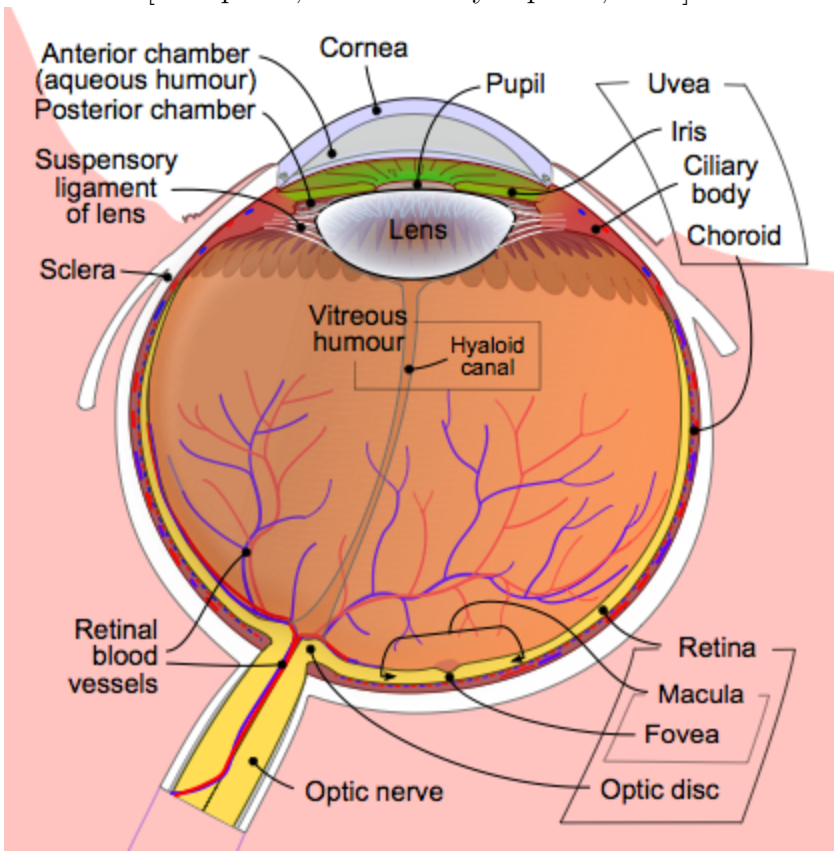
As [Hughes, 2004] said our sense organ eye,"window to the soul", is interest of lots of disciplines. (Buraya baglanti ekle) As seen on Figure 1.1 light reflected from an object enters eye in the order cornea, pupils and lenses [Fält, 2012] and focused on retina. Depends on bright or dark, or distance of object eye regulates changes like amount of lights enters eye or focus on objects with pupil and reshaping elastic lens [Kauppi et al., 2010]. (Buraya baglanti ekle)

In layers of retina, before transmitted to the brain via optic nerve for visual perception, the information in the light is processed [Kauppi et al., 2010]. These layers of retina are presented in Figure 1.2. The retina has 6 regions [Forrester et al., 2015]:

1. Central retina

Figure 1.1: Structure of eye

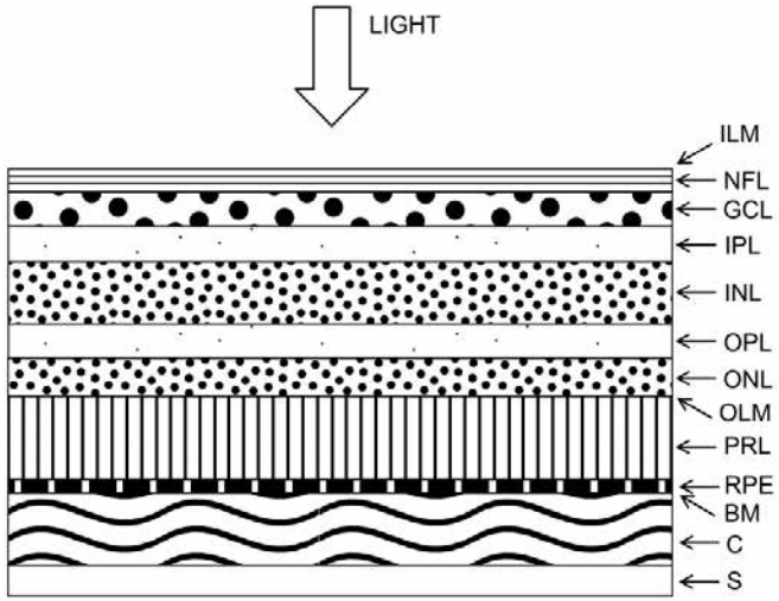
[Wikipedia, the free encyclopedia, 2007]



2. Maculalutea
3. Fovea centralis
4. Optic disk
5. Peripheral retina
6. Ora serrata

These anatomical parts of retina are represented on one of the colour fundus images in Messidor dataset [Mookiah et al., 2015] in 1.3. In this dissertation and as terms of retinal diseases, these are the terms I used.

Figure 1.2: Cross-section of retina, choroid(C) and sclera(S)



[Fält, 2012]

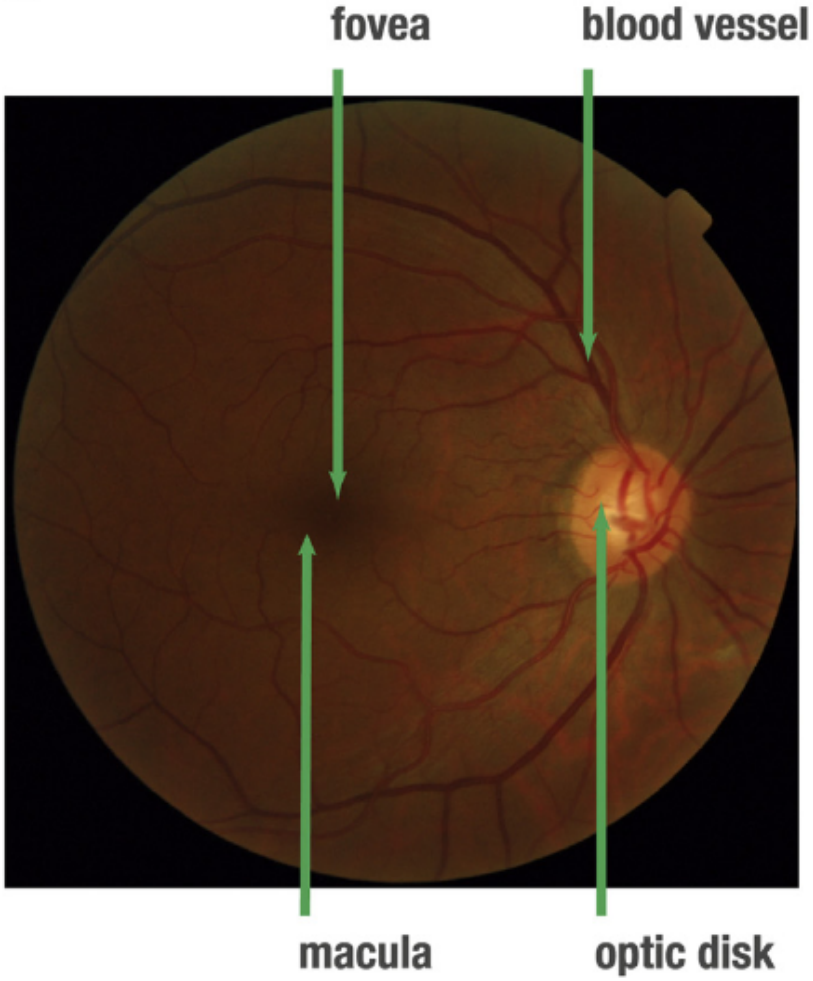
1.1.2 Diabetes Mellitus and Diabetic Retinopathy

American Diabetes Association describes diabetes mellitus, which is a considered as global epidemic [Fält, 2012], as "Group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion, insulin action, or both." [Group et al., 1979]. Diabetes mellitus can cause long term damages like on nervous system, kidneys, eye etc. Diabetic retinopathy(DR) is the most common eye disease as a result of damage on the retina of the eye triggered by diabetes mellitus and leading cause of vision loss in industrialised nations [Antal and Hajdu, 2014] [Stitt et al., 2013]. As a result of increasing number of diabetes mellitus patients, worldwide blindness caused by diabetic retinopathy will become more common if treatment of diabetic retinopathy will not improve [Wilkinson et al., 2003]. Because diabetic retinopathy if not cured on early stages of disease, it can cause the complete loss of sight [Rocha et al., 2011].

In early stages, patient does not have symptoms of diabetic retinopathy on their vision; the primary signs of DR are exudates [Nijalingappa and Sandeep, 2015]. In Figure 1.4, there is a scene from two different person; first one is normal vision and second one which has black areas on photo is the vision with advanced diabetic retinopathy [National Eye Institute(NEI), 2015].

Figure 1.3: Fundus Image

[Mookiah et al., 2015]



Diabetic Retinopathy has divided two main stages depends on abnormal new vessels existence [Tang and Kern, 2011] [Nijalingappa and Sandeep, 2015]; nonproliferative stages(NPDR) which are early stages of DR and advanced stage of DR, proliferative stage(PDR). During NPDR, DR progress in 3 stages:

1. Mild NPDR
2. Moderate NPDR
3. Severe NPDR

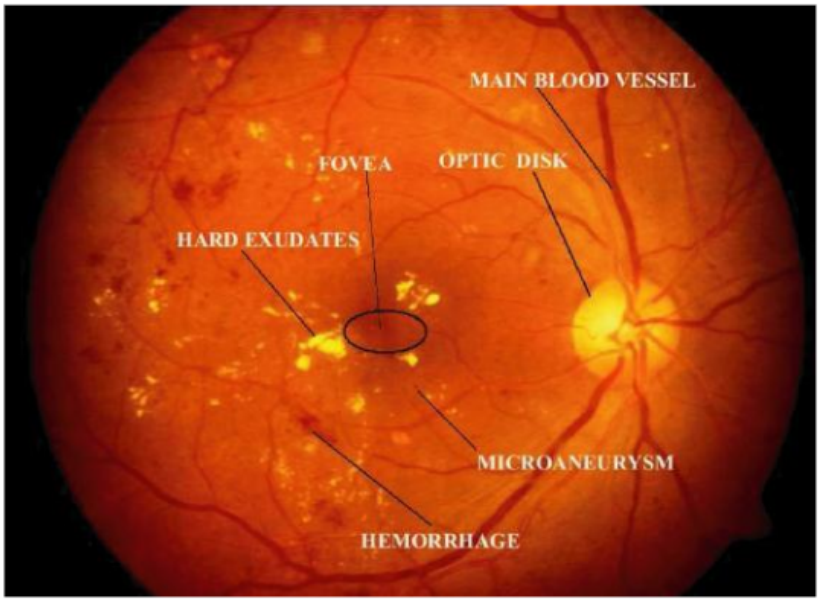
Figure 1.4: Same scene from normal vision person's eye[first] and person with advanced diabetic retinopathy[second]

[National Eye Institute(NEI), 2015] and [Wilkinson et al., 2003] defines these 4 stages of DR as follows:

- *Mild NPDR:* It is the earliest stage of DR. In retinal capillaries, small changes starts. The smallest detectable abnormalities of DR, only **microaneurysms (MA)** are detectable as small red dots.
- *Moderate NPDR:* It is the second stage of DR. Blood vessels may start to lose blood circulation ability and/or swell and distort. **Haemorrhages (HA)** starts to appear. These changes may cause diabetic **macular edema (DME)**.
- *Severe NPDR:* Vessel blockage is increased in this stage; retina starts to trigger body to develop new vessels for supplying nutrition and oxygen to suffering areas. But these vessels are fragile and thin. **Intra-retinal microvascular abnormalities (IRMA)** are also sign of this stage.
- *PDR:* In the PDR stage, **neovascularisation** which is the development of these new fragile vessels starts. These fragile vessels are dangeruous because they can cause sudden vision loss. **Soft exudates (cotton wool spots)** are visible in PDR.

Hard Exudates(HA), Haemorrhages (HA), microaneurysms (MA) presented on Figure 1.5

Figure 1.5: Hard Exudates(HA), Haemorrhages (HA), microaneurysms (MA) abnormalities on Fundus Image [Kekre et al., 2013]



1.1.3 Diagnosing Diabetic Retinopathy

In this section, I explain how diabetic retinopathy diagnoses and main methods for diagnosing DR.

Early diagnosis of DR is very important to prevent vision loss on diabetes mellitus patients [Mankar and Rout,]. Diagnosing DR is very difficult if diabetes mellitus is not suspected on patient. DR is not visible on blood samples. These make DR a deceptive disease. [Kauppi et al., 2010]. To detect DR, patient should take extensive eye exam. [Kauppi et al., 2010] grouped these examinations as follows:

- Clinical eye examination,
- Eye fundus photography,
- Fluorescein angiography,
- Optical Coherence tomography (OCT).

Since 1980s, eye fundus photography is available and it made opthalmoscopy the most commonly used examination method, if available, for diagnosis of

DR [Wendt, 2005]. Eye fundus photography lets to save the data and it helps ophthalmologists examine the image later [Hutchinson et al., 2000].

[Rocha et al., 2011] grouped diagnosing anomalies of DR in following titles and they added that diagnosing DR-non DR is recently becoming popular approach for diagnosing DR:

1. **Detection of blood vessels:** Because eye is the only place where blood vessels can directly be observed only on human body, it is unique. DR causes changes on vascular conditions in eye. Detection of any changes in the blood vessels is a way to diagnose DR on retinal fundus images. [Mendonca and Campilho, 2006]

2. **Detection of hard exudates:** Retinal oedema is the major cause of vision loss during DR progress. Existence of hard exudates, addresses the presence of retinal oedema [Singer et al., 1992] which helps ophthalmologists diagnosing and follow-up of DR. [García et al., 2009]

3. **Detection of microaneuysms:** In earliest stage of DR, microaneurysms, and hemorrhages are visible [Frank, 2004]. Hard exudates and cotton wool spots are not able to detect in early stages of DR [Navarro et al., 2016].Because it is easier to prevent DR in earlier stages, detecting microaneuysms are important.

4. **Detection of hemorrhages:** Hemorrhages are visible in early stages of DR like microaneuysms but this anomaly is more visible on advanced stages of DR; the more hemorrhages means that the more retina damage progression. In literature, the following approaches are presented for detection of hemorrhages [Rocha et al., 2011]:

   (a) Detection of blood vessels

   (b) Detection of blood vessels with hemorrhages

Algorithms and results used for these detections can be found on Related Work chapter.

1.1.4 Screening Diabetic Retinopathy

Can be extracted????

1.2 Background (?)

1.2.1 Restrictions

1.2.2 Contributions

1.3 Research Question(s)

In this work we try to answer the following research questions:

- Can signs of DR can be detected automatically by using machine learning algorithms especially by using deep learning methods?
- Can we detect signs of DR in a dataset by using another dataset's trained model?
- Will using deep learning on the task of detection of DR open new research directions in this area?

1.4 Motivation

According to Natinal Eye Institute only in USA around 40-45% of people having diabetes were diagnosed with diabetic retinopathy. Besides, nearly 35% of people having diabetes in worldwide have DR and 1 in 10 will have a vision threatening form of the disease [Yau et al., 2012]. According to a recent work diabetic retinopathy effects almost 4% of people of Europe also. [Nentwich and Ulbig, 2015] Therefore, it is essential to detect the signs of DR in the early stages. The process to detect the signs of diabetic retinopathy needs trained technicians to work on the eye images, analyse. Our main motivation is to make this process automatic by using convolutional neural networks.

1.5 Aims and Objectives

As clearly explained in the previous sections, our main aim and goal is the automatic detection of the early signs of DR by using one of the widely used deep learning methods, convolutional neural networks. We look for the results of using a big dataset as training data and other available public datasets as test datasets.

1.6 Reports Structure

The structure of this work is as follows: first we review the ralated work in the next section, then we explain our methodology and give experimental setup and the result of the experiments. Finally we conclude our work.

Chapter 2

Related Work

Details what others have done that is relevant to your work. 1.

1. Objectives
2. Describe the context of the research question in detail, defining terminology, and with references.
3. Explain how the problem, or related problems, has been solved previously. Critically analyze existing solutions. Discuss how your approach compares to these solutions.
4. Explain other techniques that you have used to: help understand and analyze the research question; motivate your own work; evaluate your solution.

2.1 Objectives

A single sentence that describes the purpose of this section.

2.2 Eye Disease Datasets

2.2.1 Feature Datasets

- Clinical trial dataset'e bak - From Messidor fundus image, extracted features

2.2.2 Diabetic Retinopathy Fundus Image Datasets

[Kauppi et al., 2013], addressed [Thacker et al., 2008]'s 8 key questions for 6 publicly available fundus image databases. These questions are:

1. How is testing currently performed?
2. Is there a data set for which the correct answers are known?
3. Are there data sets in common use?
4. Are there experiments which show algorithms are stable and work as expected?
5. Are there any strawman algorithms?
6. What code and data are available?
7. Is there a quantitative methodology for the design of algorithms?
8. What should we be measuring to quantify performance? What metrics are used?

In his research, he compared these 6 databases and summarised them depends on amount of these addressed questions[Kauppi et al., 2013]. Also, in his thesis he established DIARETDB1 database by means of these key questions.

In this section, I give information about some of the publicly available fundus image databases.

DRIVE (Digital Retinal Images for Vessel Extraction)

DRIVE data set constructed by [Staal et al., 2004]. DRIVE data set includes 40 manually labelled retinal images for training and evaluation of [Staal et al., 2004]'s method which are randomly selected from 400 diabetic subjects between 25-90 years of age as a part of a screening programme in the Netherlands. Images labelled by 3 human observers who were trained by experienced ophthalmologist. 7 of these manually labelled retinal images has DR indications and 33 of them not.

DRIVE addresses 7 of [Kauppi et al., 2013]'s key questions which is one of the best results if you compare with the other 6 databases. It makes publicly available DRIVE very popular in automated diabetic retinopaty detection environment.

General information about DRIVE database:

- **Availability date:** 2004
- **Size:** 40 retinal images
- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view
- **Resolution:** 768 by 584 pixels

STARE (STructured Analysis of the Retina)

Stare database contains 400 publicly available raw images which can be obtained from STARE website [Hoover, 2013]. They also gives a list of information about diagnosis of these images. They also shared 20 hand labelled images for blood vessel segmentation [Hoover et al., 2000] extracted from these 400 images. Because I can obtain DR, non-DR information from diagnosis list. There are 13 diagnosis which represented with numbers in the list. The images which has DR diagnosis represented with 7 and 8 which addresses Background Diabetic Retinopathy(BDR/NPDR) and Proliferative Diabetic Retinopathy(PDR). These diagnosis and their diagnosis numbers

can be found on appendix. APPENDIX EKLE!!!! - diagnosis listesini ve image-diagnosis listesini.

General information about STARE database:

- **Availability date:** 2004
- **Size:** 20 retinal images
- **DR Size:** 10 retinal images
- **Non-DR Size:** 10 retinal images
- **Camera:** TopCon TRV-50 fundus camera
- **Resolution:** 605 by 700 pixels

CHASE (Child Heart And Health Study in England)

General information about CHASE database:

- **Availability date:** 2004
- **Size:** 40 retinal images
- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** NM-200-D fundus camera made bu Nidek Co. Ltd., Gamagori, Japan
- **Resolution:** 1280 by 960 pixels

ROC

General information about ROC database:

- **Availability date:** 2004
- **Size:** 40 retinal images

- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view
- **Resolution:** 768 by 584 pixels

CMIF

General information about CMIF database:

- **Availability date:** 2004
- **Size:** 40 retinal images
- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view
- **Resolution:** 768 by 584 pixels

REVIEW

General information about REVIEW database:

- **Availability date:** 2004
- **Size:** 40 retinal images
- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view
- **Resolution:** 768 by 584 pixels

DIARETDB

General information about DIARETDB0 database:

- **Availability date:** 2004
- **Size:** 40 retinal images
- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view
- **Resolution:** 768 by 584 pixels

General information about DIARETDB1 database:

- **Availability date:** 2004
- **Size:** 40 retinal images
- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view
- **Resolution:** 768 by 584 pixels

General information about DIARETDB2 database:

- **Availability date:** 2004
- **Size:** 40 retinal images
- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view
- **Resolution:** 768 by 584 pixels

MESSIDOR

General information about MESSIDOR database:

- **Availability date:** 2004
- **Size:** 40 retinal images
- **DR Size:** 7 retinal images
- **Non-DR Size:** 33 retinal images
- **Camera:** Canon CR5 non-mydriatic 3CCD camera with a 45 degree field of view
- **Resolution:** 768 by 584 pixels

2.3 Machine Leearning Approaches for Diabetic Retinopathy

2.3.1 Other Approaches

2.3.2 Neural Network Approaches for Diabetic Retinpathy

Chapter 3

Solution

1. often the name of your solution - details what you have done and how you have done it.
2. objectives - a single sentence that describes the purpose of this section
3. provide an analysis of the problem , motivating your approach to answering the research question.
4. Explain your approach by describing exactly what you have done.
5. Explain how you have achieved your solution. Examples: explain how a process improvement was implemented, how a mathematical technique was derived, or how an algorithm was implemented.

3.1 Background

3.1.1 Deep Learning

Deep Learning is defined as:
"A class of machine learning techniques that exploit many layers of non-linear information processing for supervised or unsupervised feature extraction and transformation, and for pattern analysis and classification." in the book Deep Learning methods and Applications [Deng and Yu, 2014]. In this work we investigate the effects of using Deep Learning techniques for the task of finding the signs of diabetic retinopathy and for this task we use a special type

Figure 3.1: withDR

of Artificial Neural Networks called Convolutional Neural Networks that we will explain in detail in the following sections.

3.1.2 Neural Networks

Neural Networks are computational models that are based on the brain architecture to solve different type of problems like image recognition, anomaly detection, signal processing etc. [Shiffman et al., 2012] Basically a neural network is an architecture that has a set of input neurons that are activated by inputs (like pixel RGB values for images) and those inputs are weighted and transformed to the other neurons until the architecture arrives the final output neurons.

Figure 3.3 shows the similarity between the brain neuron architecture and neural network architecture.

3.1.3 Convolutional Neural Networks

Convolutional Neural Networks(CNNs) are a type of feed forward neural networks that are based on the animal visual cortex. (http://deeplearning.net/tutorial/lenet.html)

Figure 3.2: withoutDR

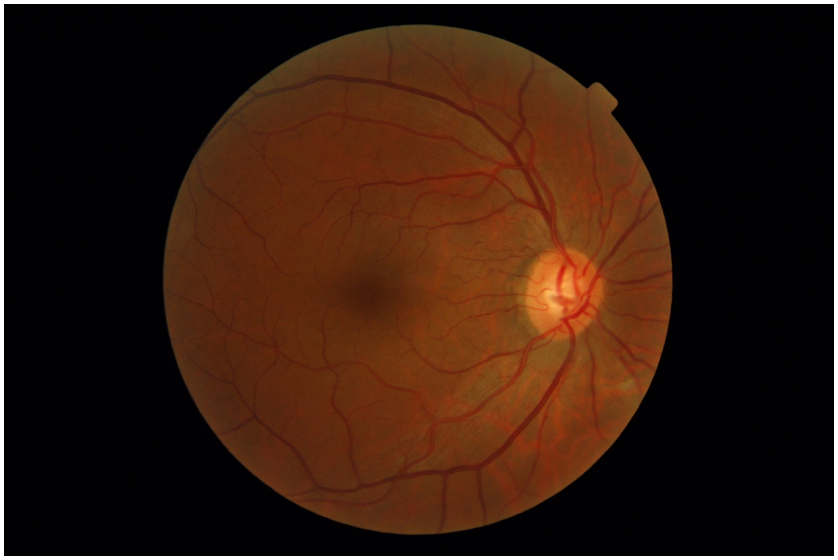


Figure 3.3: Neural Network

CNNs are widely used in different applications of Deep Learning. Like regular NNs CNNs also have neurons that have weights and biases that can be learned. The main different between regular NNs and CNNS is that CNNs make the forward function more efficient and creates the neural network architecture with smaller number of parameters learned, which is a lot more efficient. (REF: http://cs231n.github.io/convolutional-networks/)

In Figure 3.4 a regular neural network architecture can be seen and in Figure 3.5 shows a sample CNN architecture.

CNNs are made of different layers that feedforward the activation of the input neurons to the following layers.The layers are as follows:

1. Convolutional Layer

Figure 3.4: Regular Neural Network

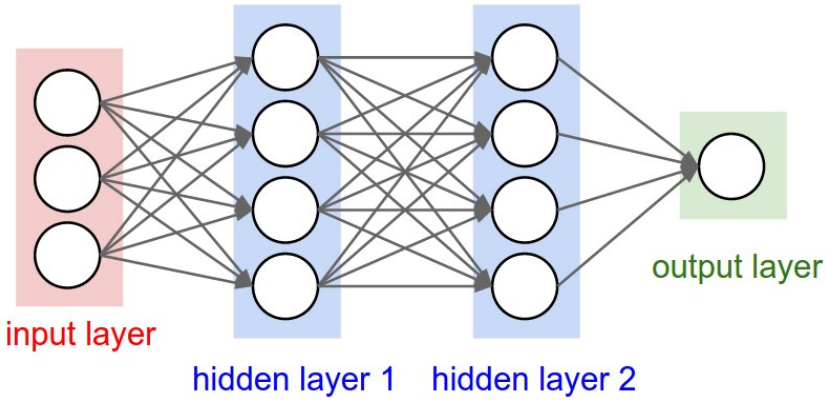
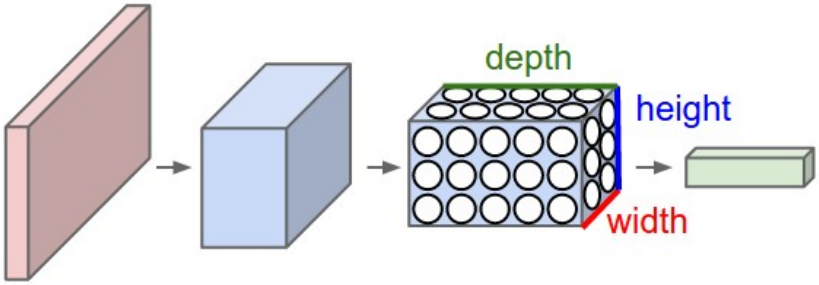


Figure 3.5: Convolutional Neural Network



2. Pooling Layer

3. Fully Connected Layer

To explain the details of the layers of the CNNs we will use a simple CNN architecture for diabetic retinopathy detection problem. Notice that later we will explain the final CNN architecture we use for the classification problem which will have lots of different layers and parameters etc. For now to explain how CNNs are used for detection of signs of diabetic retinopathy we use the following CNN architecture:
$INPUT => CONV => RELU => POOL => FC$.

- INPUT[128x128x3] has the pixel values of the image after preprocessing stage, in our example it is an input image with width 128, height 128 and depth 3.

- CONV layer transforms the pixel values of the local regions of the input image by using input neurons' weight and biases. After CONV layer if we use 32 filters, we will have [128x128x32] volume.
- RELU layer applies an activation function to the output of CONV layer that does not change the volume [128x128x32]
- POOL layer downsamples the width and height dimensions of the volume resulting in [64x64x32].
- FC layer classifies the input image to one of the classes (DR and NoDR) resulting in [1x1x2] which has two class scores. Notice that if our problem was to classify input image to 4 classes the output volume would be [1x1x4].

3.1.4 TensorFlow

TensorFlow is a machine learning library opensourced by Google for distributed machine learning and deep learning. In this work for convolutional neural networks we use Google's Tensorflow library. (https://www.tensorflow.org)

3.2 Datasets

3.2.1 Messidor Dataset

The main dataset that we use is called Messidor Dataset [Decencire et al., 2014] that contains 1200 eye fundus color numerical images. They used a color video 3CCD camera on a Topcon TRC NW6 non-mydriatic retinograph with a 45 degree field of view to capture the images using 8 bits per color plane at 1440*960, 2240*1488 or 2304*1536 pixels. They have two medical diagnoses in the dataset: retinopathy grade and risk of macular edema.

Different retinopathy grades are shown in Table 3.1 where MA: number of microaneurysms, H:number of hemorrhages, NV = 1: neovascularization and NV = 0: no neovascularization.

Different level of macular edema risk are shown in Table 3.2.

Table 3.1: Retinopathy Grade

grade	explanation
0	$(MA = 0)AND(H = 0)$
1	$(0 < MA <= 5)AND(H = 0)$
2	$((5 < MA < 15)OR(0 < H < 5))AND(NV = 0)$
3	$(MA >= 15)OR(H >= 5)OR(NV = 1)$

Table 3.2: Risk of Macular Edema

risk	explanation
0	(No risk): No visible hard exudates
1	Shortest distance between macula and hard exudates ¿ one papilla diameter
2	Shortest distance between macula and hard exudates ¡= one papilla diameter

3.3 Preprocessing

Before training the convolutional neural networks the first thing to do is preprocessing the images. Preprocessing is a must stage since the images in the dataset are produced under different circumstances. For instance not all images have the same resolution and not all of the images are produced under the same lightning. To fix these problems we apply some preprocessing techniques for the images.

1. Blur the images. Blurring the images is a technique in Computer Vision problems that is used for enhancing image structures at different scales.
2. Cropping the images to bounding box having pixel values above a threshold.
3. Scaling the images to a certain resolution. In our case we scale all of the images to 128x128.
4. We apply histogram normalization for each of the RGB channels seperately. Histogram normalization changes the pixel intensity values. This results in areas of lower local contrast gaining a higher contrast by effectively spreading out the most frequent intensity values.

TODO: Rotate the images randomly, both test and train data. Aplly contrast, sharpness etc to the images and compare the results. Add here an image with different preprocessing steps.

Table 3.3: CNN architecture

layer	input volume	no of filters	nof units
conv	128x128x3	16	
conv	128x128x16	16	
pool	128x128x16		
conv	64x64x16	32	
conv	64x64x32	32	
pool	64x64x32		
conv	32x32x32	64	
conv	32x32x64	64	
pool	32x32x64		
conv	16x16x64	128	
pool	16x16x128		
conv	8x8x128	128	
pool	8x8x128		
conv	4x4x128	256	
pool	4x4x256		
dropout	2x2x256		
fc1	2x2x256		96
fc1	96x2		2
softmax			

3.4 ConvNET Architecture for Diabetic Retinopathy

In this section we will explain the convolutional neural network used in this work for diabetic retinopathy detection architecture in detail.

Table 3.3 shows the details of the convolutional neural network architecture used for this work. Notice that for the number of units after the second fully connected layer, 2 represents number of output classes, in this case DR and noDR. For the degree of the diabetic retinopathy it would be 4. For all of the convolutional layers stride size is 1 and padding is the same, meaning that the dimension (width, height) does not change. Kernel size for conv layers is always 3x3 in this work. Pool layers use maxpooling with 2x2 pooling window and stride is 2, such that after pooling layer width and height is divided by 2. After all convolutinal layers for the activation rectified linear unit (ReLU) is used. (buraya relu image gelecek ve formul) Similarly after the

fully connected layer also ReLU is used. We trained the net using adam optimizer (a method for stochastic optimization) [Kingma and Ba, 2014] with logloss as a loss function.

Chapter 4

Evaluation

1. evaulates your work(both in absolute terms, and compared to other solutions)
2. objectives
3. explain what was evaluated or validated
4. experimetal setup - detail how you evaluated and validated your work.
5. present your results clearly and objectively, without interpretation - ideally with graphs(data)
6. explain your results - ideally with explanatory text(analysis) to both explain the meaning of these results, and provide the reasons for why these particular results were obtained
7. critically analyze your results. Identify the contents in which your results are relevant and any threats are to the validity of your results. Show how well you have answered the research question.
8. Critically analyze your results with respect to the "Related Work" presented earlier.

In this section we explain the experimental setup, experimental results and discuss the results of the several experiment conducted in detail.

4.1 Experiments with Messidor Dataset

4.2 Experiments by using other datasets

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