PharmaSUG 2021 - Paper AI-010

Integrating Digital Images for Ophthalmology Trials using Machine Learning Techniques for Image Analysis

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ABSTRACT

Ophthalmology related clinical trials often involve high levels of risk due to issues concerning patient safety. With the advancement of imaging techniques, there is an increasing abundance of patient data available for the purpose of research. For every patient, an ophthalmic visit consists of various data points collected related to visual acuity, contrast sensitivity, ocular pressure, visual field tests, and retinal scans with the optic nerve. Measurements are observed and recorded in every visit while data may be processed and mapped for clinical research studies. While, the rest of the vision related parameters may be directly inputted by a physician, there is a lot of imaging data that can be standardized and made available for researchers. This paper would be focused on acquiring retinal scan data for patients, analyzing images, detecting abnormalities, and integrating them into clinical trials. Retinal scans will be analyzed to find anomalies and help with disease detection using image processing and machine learning techniques. This approach will be useful for capturing images and extracting the exact location and dimensions of diseased areas from images. The data can then be mapped as per standards for clinical research.

INTRODUCTION

In this paper we will explore the eye and list out the Ophthalmology checks performed at physician's office along with tools and techniques utilized for Image analysis, using MATLAB (MathWorks) as a tool used for computer vision.

EXPLORING THE HUMAN EYE

The Human Eye is a complex machine of various parts that resemble a camera, where all image formation happens at the Macula or the Central Vision.

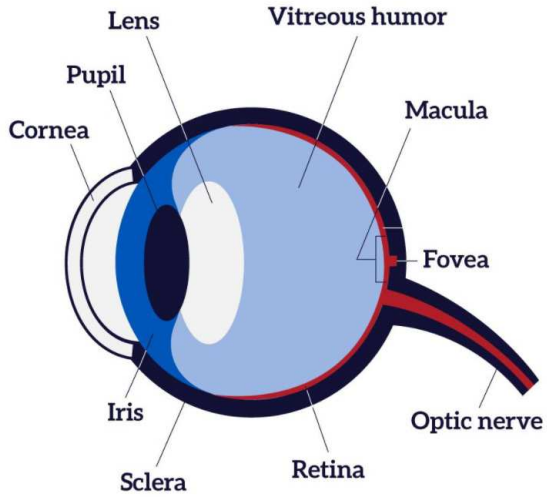


Figure 1a: Parts of the Human Eye

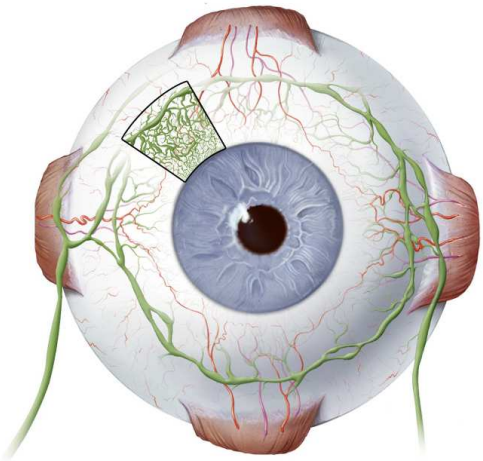


Figure 1b: The Human Eye Anatomy

Figure 1: The Human Eye: Morphology. Image Source: National Eye Institute (NEI)
Figure 1a: How the eyes work. 2019. https://www.nei.nih.gov/learn-about-eye-health/healthy-vision/how-eyes-work
Figure 1b: NEI-medialibrary-5261899.jpg. 2020. https://medialibrary.nei.nih.gov/media/3723

COMPONENTS OF OPHTHALMOLOGY DATA

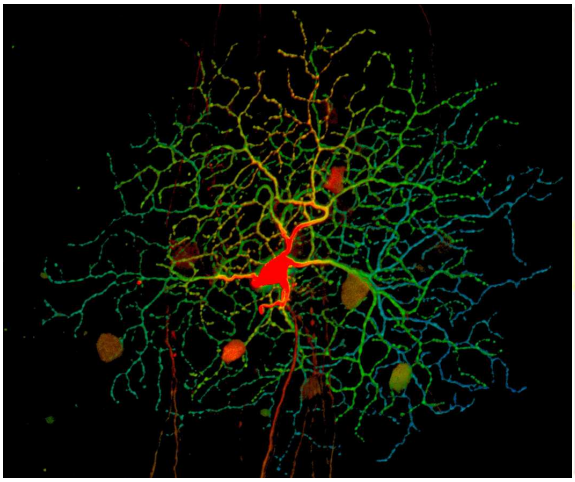
Some of the basic checks performed during an annual eye check-up are:

TEST	REQUIRES MEASUREMENT/DATA
• **Auto refractor**	• Yes
• **Eye Dilation**	• No
• **Glaucoma Test**	• Yes
• **Ophthalmoscope**	• Yes
• **Optomap.**	• Yes
• **Peripheral Vision Test**	• Yes
• **Phoropter**	• Yes
• **Puffer Test**	• Yes
• **Retinoscope**	• No
• **Slit Lamp Exam**	• No
• **Snellen Chart**	• Yes
• **Vision Screening**	• Yes
• **Vision Testing**	• Yes

Figure 2: Ophthalmology Data Collection.

IMAGING DATA IN OPHTHALMOLOGY

One of the most important part of Ophthalmology data collection involves imaging data or retinal scans. Retinal Fundus scans are utilized for analysis and change from baseline tracking. Retinal ganglion cells receive information about the light our eyes detect from other cells in the retina at structures called dendrites and then relay it to the brain via axons.



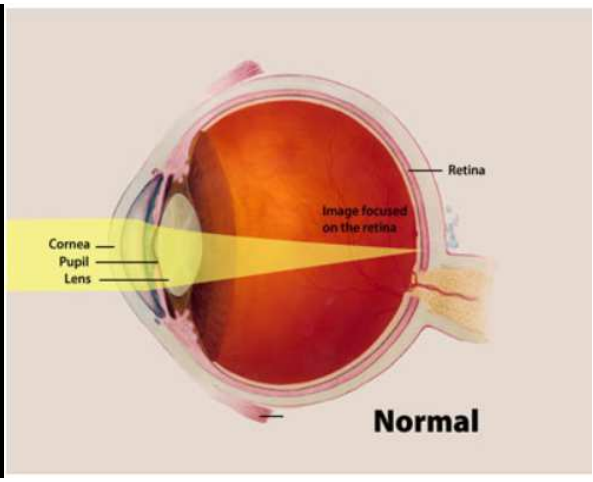


Figure 3a: The Human Retina Figure 3b: Normal Vision

Figure 3: An illustration of the human retina. Image source: National Eye Institute (NEI).

Figure 3a: NEI-medialibrary-3315734.jpg. 2019. https://medialibrary.nei.nih.gov/media/3497
Figure 3b: NEI-medialibrary-6928570.png. 2019. https://medialibrary.nei.nih.gov/media/1804

DEEP DIVE INTO RETINAL IMAGE ANALYSIS

We will be analyzing retinal scans data, obtained from the National Eye Institute image library. The images have been downloaded, saved at the local directory, and read into MATLAB environment.

READING RETINAL SCAN IMAGES

All images are in *.png format and each image has three components, Red, Green Blue

```
one=imread('one.png'); two=imread('two.png');
three=imread('three.png'); four=imread('four.png');
five=imread('five.png'); six=imread('six.png');
seven=imread('seven.png'); eight=imread('eight.png');
imshow(two);
% Eight images are read (ordered from left to right) .
```

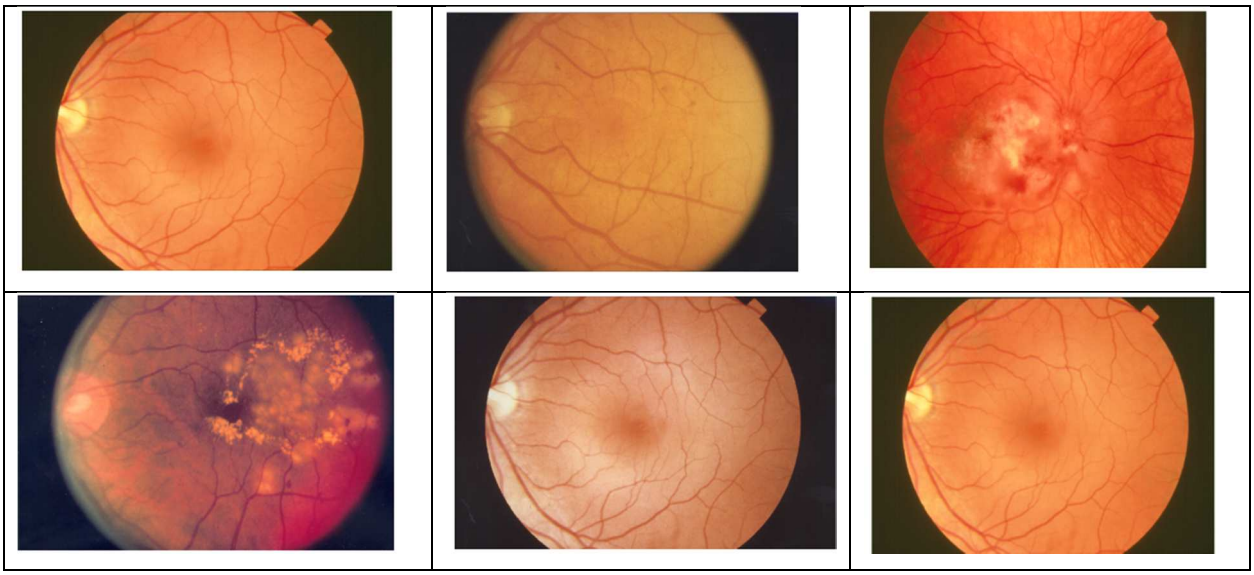


Figure 4: Reading source image data files in *.png format.

Image Source: National Eye Institute (NEI).

1. NEI-medialibrary-1207347. 2019. https://medialibrary.nei.nih.gov/media/3556
2. NEI-medialibrary-9842539.png. 2020. https://medialibrary.nei.nih.gov/media/3815
3. NEI-medialibrary-6983558.png. 2019. https://medialibrary.nei.nih.gov/media/3555
4. NEI-medialibrary-6545533.png. 2019. https://medialibrary.nei.nih.gov/media/3542
5. NEI-medialibrary-6879455.png. 2019. https://medialibrary.nei.nih.gov/media/3552
6. NEI-medialibrary-1499432.png. 2020. https://medialibrary.nei.nih.gov/media/3825

OBTAIN IMAGE INFORMATION AND PRE-PROCESS IMAGES

Images may be of similar size in the real world, here they are all different sizes.

Check Image size:

```
%Check Image Size
title 'Check Image Size'
size(one)
size(two)
size(three)
size(four)
size(five)
size(six)
size(seven)
size(eight)
```

```
ans = 1×3
     434    617      3

ans = 1×3
     434    617      3

ans = 1×3
     649    972      3

ans = 1×3
     430    651      3

ans = 1×3
     646    974      3

ans = 1×3
     650    958      3
```

RESIZE AND PRE-PROCESS IMAGES FOR ANALYSIS

We would need to standardize the images to be of same size for comparison, contrast, and analysis. Images would then need to be converted from 3D (RGB) to 2D (Grayscale). RGB images are 3 dimensional arrays of Red, Green and Blue pixels,

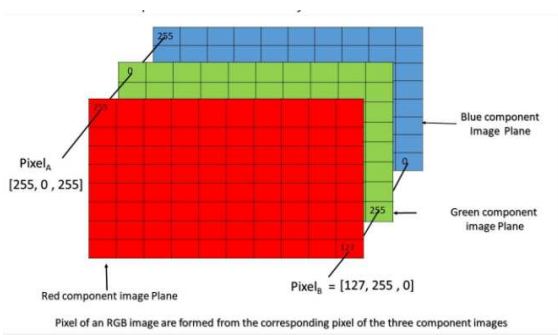


Figure 5a: RGB Image

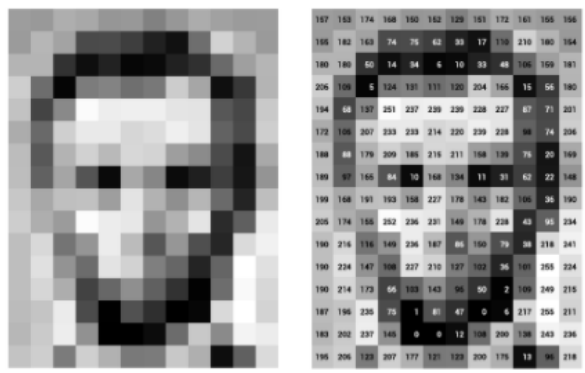


Figure 5b: Grayscale Image

Figure 5a: MATLAB: RGB image representation. (2018, June 26). https://www.geeksforgeeks.org/matlab-rgb-image-representation/

Figure 5b: Stanford Artificial Intelligence Laboratory. https://ai.stanford.edu/~syyeung/cvweb/tutorial1.html

```
%Resize Images one standard size
```

```
title 'Resize Images'
one_1=imresize(one,[430,617])
two_1=imresize(two,[430,617])
three_1=imresize(three, [430,617])
%Convert the image from RGB to Grayscale
title 'Convert the image from RGB to Grayscale.'
One_2=rgb2gray(one_1);
Two_2=rgb2gray(two_1);
```

```
Three_2=rgb2gray(three_1);
imshow(One_2);
```

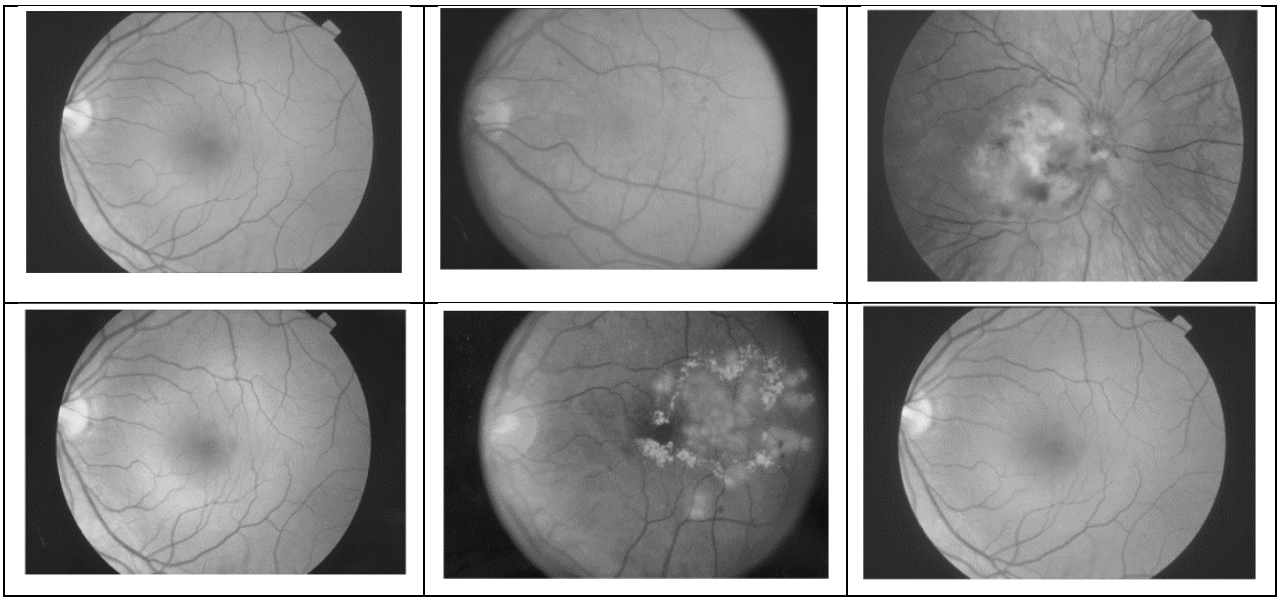


Figure 5: Converting images from RGB to Grayscale.

CONTRAST ADJUSTMENT

Images are contrast adjusted using three methods, imadjust which will either auto adjust or readjust based on input and output contrast parameters. Here we are displaying three methods of image contrasting that use the auto adjust(imadjust) and using intensity values, by using intensity values in empty matrix ([]) for [low_in high_in] or for [low_out high_out], this would specify to a default of [0 1].

```
One_2=imadjust(One_2);
One_2_A=imadjust(One_2,[0.2 0.9],[]);
One_2_B=imadjust(One_2,[0.2 0.9],[0.0 0.9]);
imshow(One_2) % Results Left to Right
```

Figure 6: Adjust Image Contrast

```
%Adjust image Contrast by image histogram equalization for unclear images
%here we are considering the Sixth Image
figure
imhist(Six_2,64)
```

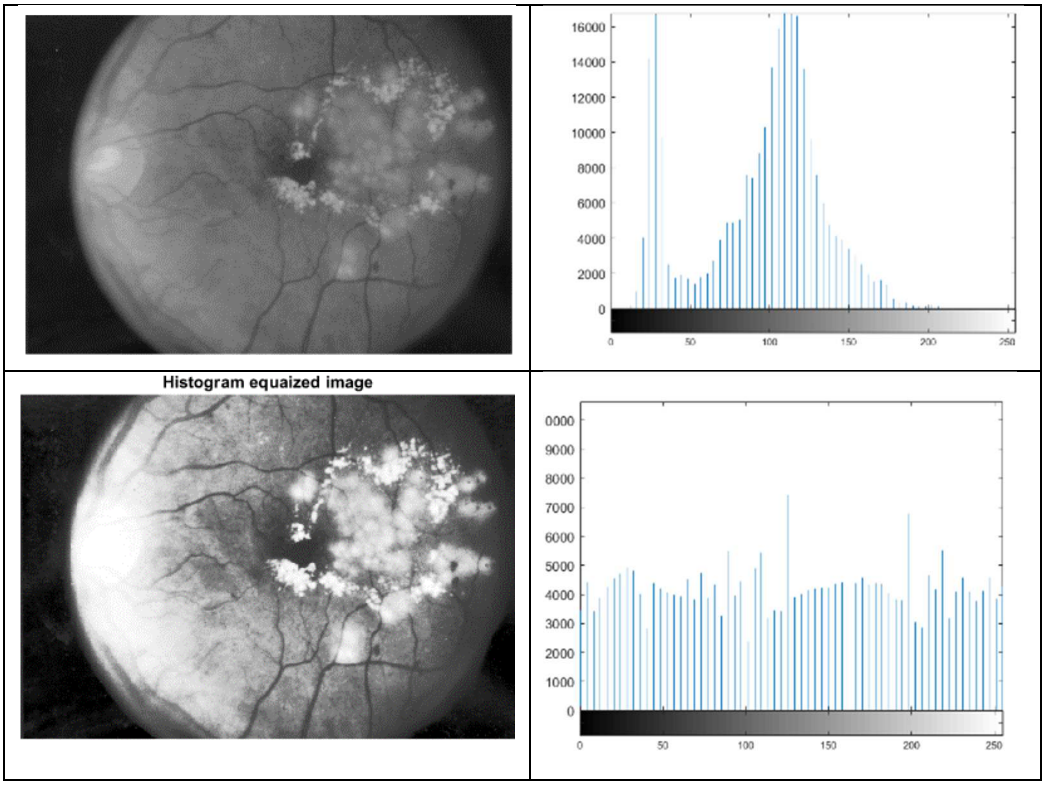


Figure 7: Adjust Image Contrast by Histogram equalization

IMAGE DIFFERENCING TO IDENTIFY PROBLEM AREA

SECTION A

In this section two grayscale images are subtracted to get the diseased area, this method can be applied to calculate change from previous visit.

```
%Select two images to compare - substracting abnormal image from normal
%image
imshowpair(One_2_A,Four_2_A,'montage');
SubtractedImage = double(One_2_A) - double(Four_2_A);
imshow(SubtractedImage, []);
title 'Substracted Image with abnormality in dark area - Change from baseline'
Sub=imadjust(SubtractedImage);
imshow(Sub)
title 'Substracted Image with abnormality in black area'
%Contour of the Source and differenced Image
Normal= imcontour(One_2);
Abnormal= imcontour(Four_2);
```

```
Sub_Contour=imcontour(SubtractedImage);
imshow(Sub_Contour)
```

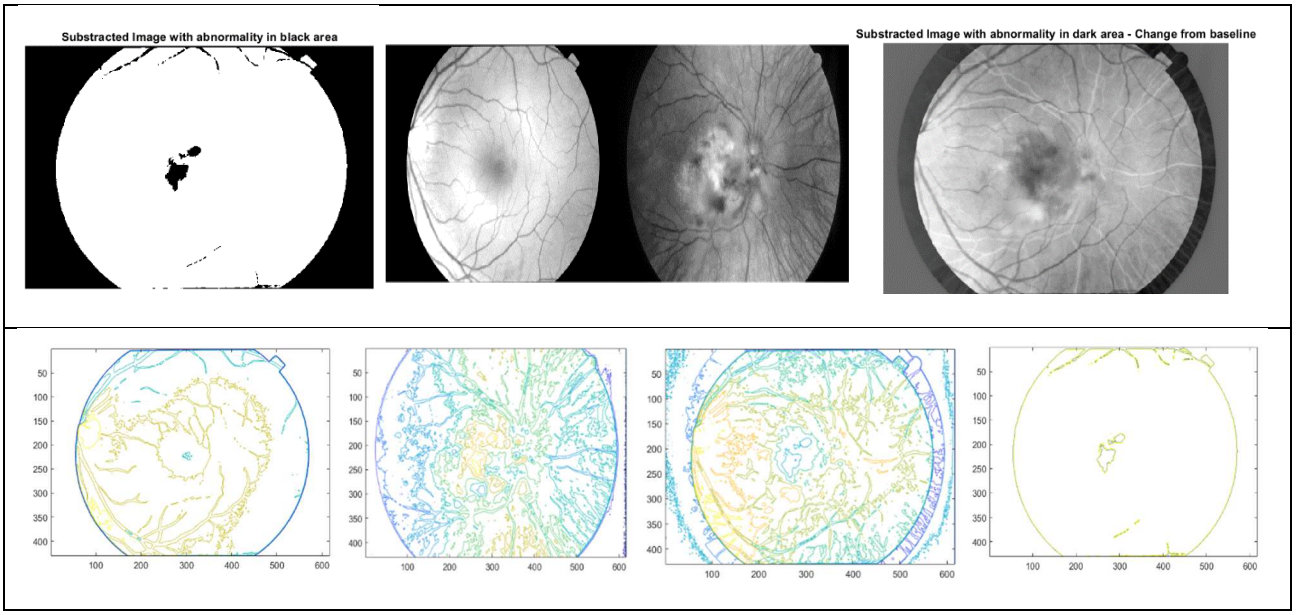


Figure 8: Differencing two images, abnormal from normal

SECTION B

Like previous section images can be converted to binary format to perform differencing. Image contours outline the diseased area.

```
%Select other two images to compare - substracting abnormal/diseased image from
normal eye scan %image conversion to binary
a=im2bw(one_1,0.5); b=im2bw(six_1,0.5);
imshowpair(one_1, six_1,'montage');
SubtractedImage2 = double(a) - double(b);
imshow(SubtractedImage2, []);
title 'Substracted Image 2 with abnormality in dark area - Change from
baseline'
Normal1= imcontour(a);
Abnormal1= imcontour(b);
Sub_Contour2=imcontour(SubtractedImage);
```

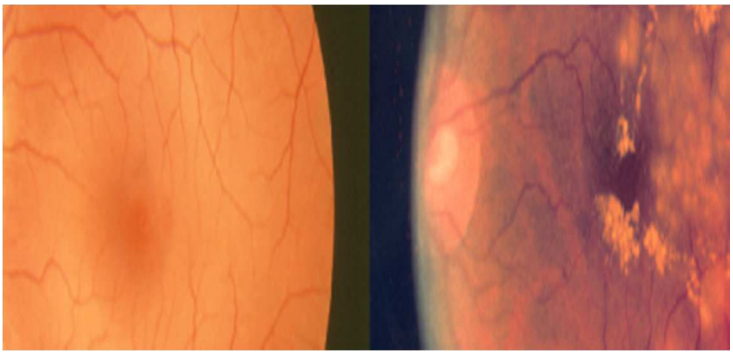
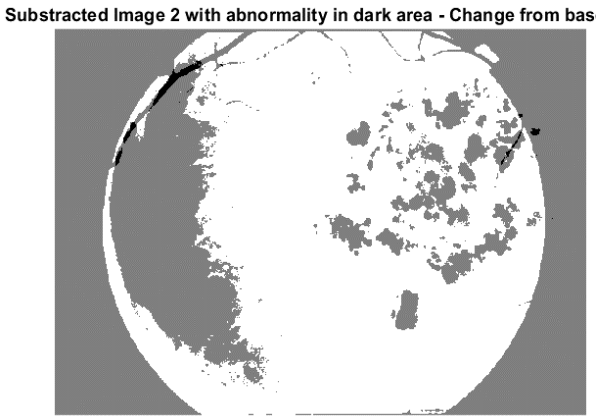
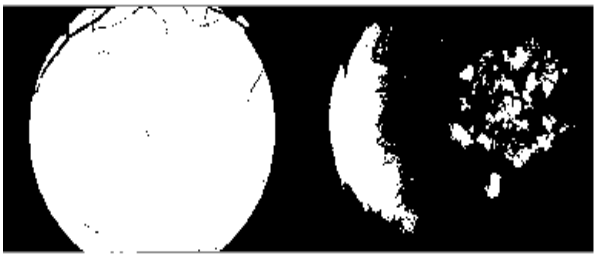
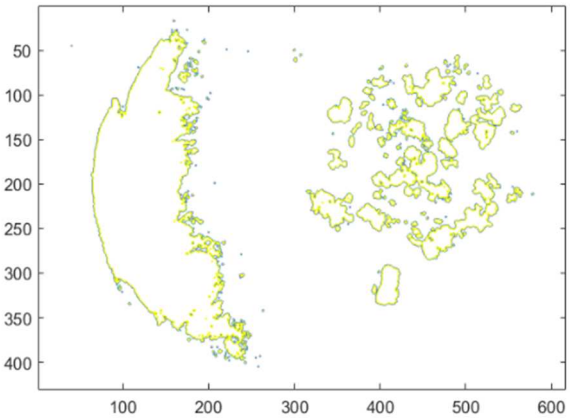


Image Source:

1. NEI-medialibrary-1207347. 2019. https://medialibrary.nei.nih.gov/media/3556
2. NEI-medialibrary-6545533.png. 2019. https://medialibrary.nei.nih.gov/media/3542







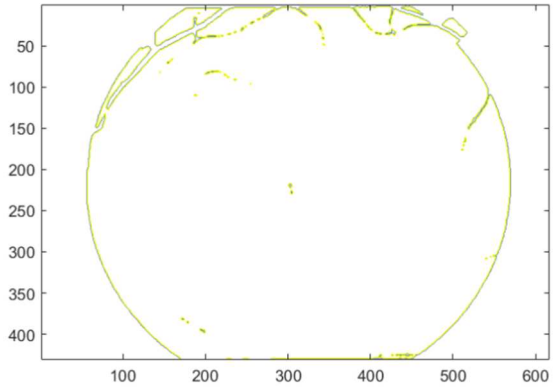


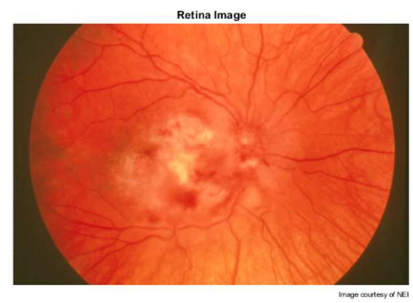
Image difference above displays diseased area boundary. Images on the left display image contours of the subtracted image and the contrast adjusted image to display rest of the scanned area.

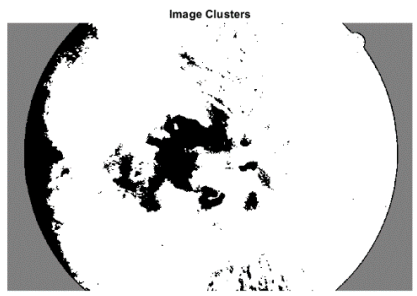
Figure 9: Image differencing on binary images

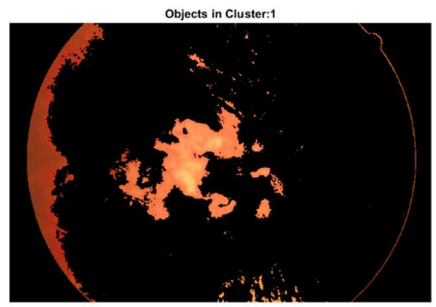
COLORED IMAGE SEGMENTATION WITH K-MEANS CLUSTERING

One of the methods of image segmentation is K-means clustering where each image is segmented into a set of regions with similar pixel or groups that are close.

```
Image = imread('Four.png');
imshow(Image), title('Retina Image');
text(size(Image,2),size(Image,1)+15,...
     'Image courtesy of NEI',  ...

'FontSize',7,'HorizontalAlignment','right');

%Get Clusters
colors_Image = rgb2lab(Image);
imshow(colors_Image)
Colors = colors_Image(:,:,2:3);
ab = im2single(Colors);
nColors = 3;
% repeat tImage clustering 3 times
pixel_colors =
imsegkmeans(ab,nColors,'NumAttempts',3);
imshow(pixel_colors,[])
title('Image Clusters');

%Get Objects in First Cluster
mask1 = pixel_labels==1;
cluster1 = Image .* uint8(mask1);
imshow(cluster1)
title('Objects in Cluster:1');


%Get Objects in Second Cluster
mask2 = pixel_labels==2;
cluster2 = Image .* uint8(mask2);
imshow(cluster2)
title('Objects in Cluster:2');


%Get Objects in Third Cluster
mask3 = pixel_labels==3;
cluster3 = Image .* uint8(mask3);
imshow(cluster3)
title('Objects in Cluster:3');
```







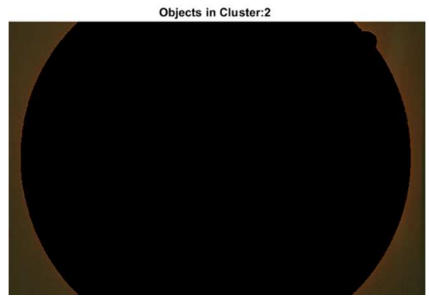


Image Source: NEI-medialibrary-6983558.png. 2019. https://medialibrary.nei.nih.gov/media/3555

Figure 10: Image segmentation with K-Means Clustering

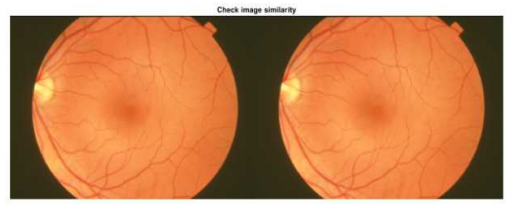
IMAGE METRICS AND ANOMALY MEASUREMENT

1. Distinguish similar images by Mean square error method on RGB images.

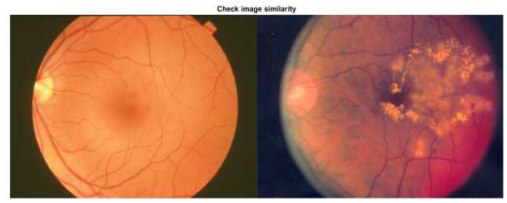
Colored Images: Based on Mean Square Error which is defined as Mean or Average of the square of the difference between actual and estimated values of pixel intensities images can be classified as similar or different.

```
imshowpair(one_1,seven_1,'montage
');
title 'Check image similarity';
error_1=immse(one_1, seven_1)
imshowpair(one_1,six_1,'montage')
;
title 'Check image similarity';
error_2=immse(one_1, six_1)
```

Figure 11: Measure image Similarity based on error values.



error_1 = 0



error_2 = 2.4596e+03

2. Distinguish similar images by Image correlation on 2D/Grayscale images.

Image may be compared by computing the correlation coefficient between two images, a value closer to 1 indicates closer correlation between images.

```
R = corr2(One_2, Two_2)
```

R = 1, R1 = corr2(One_2, Four_2) R1 = 0.6903

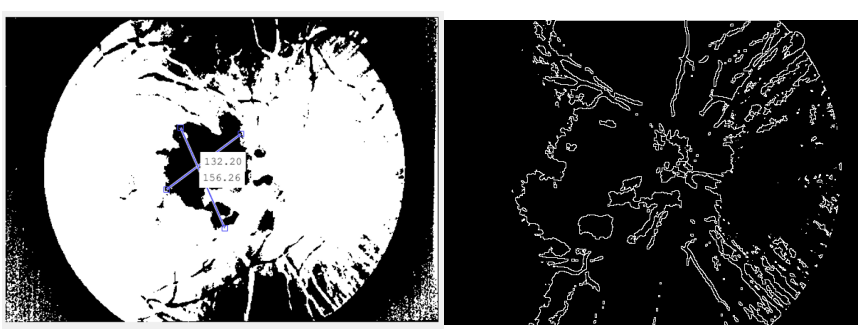
3. Pixel to centimeters conversion

As per standard conversions pixels may be translated to centimeters[10]:

1 pixel (X) = 0.0264583333 cm, 1 cm = 37.7952755906 pixel (X)

4. Dimensions Measurement

One of the methods of image dimension measurement is by using the Image processor tool in MATLAB, this helps to dynamically estimate distance between two points and dimensions of diseased area.



The area of the human retina is about 1,094 square mm, therefore all measurements need to be readjusted/scaled by the imaging device and the image resolution and the average dimension of the human eye is 22 mm from anterior to posterior poles[15].

Figure 12: Measure diseased area and perimeter

5. Area Calculation

bwarea(One_2), bwperim(BWH,8); gives area and perimeter of the images in binary format, which will be based on image dimensions: area = 264839 sq. pixels. Divide by 1428.84 to get area in sq. cm.

MAPPING DATA FROM IMAGES TO STANDARD FORMAT FOR ANALYSIS

Measurements can be grouped to: General Eye checkups and Eye related Imaging data based on anterior (example: Lens, Cornea, Iris) or posterior chamber of the eye (example: Retina).

Physiological ophthalmic examinations, OE Domain

Row #	STUDYID	DOMAIN	USUBJID	FOCID	OESEQ	OETESTCD	OETEST	OEORRES	OEORRESU	OETRESC	OESTRESN	OELOC	OELAT	OEMETHOD
1	XYZ	OE	XYZ-AB-333-009	OD	1	OEEXAM	Ophthalmic exam	NORMAL		NORMAL		LENS	RIGHT	SLIT LAMP

OEVAL	VISITNUM	VISIT	OEDTC
INVESTIGATOR	1	SCREENING	2022-10-19

Ophthalmology related Imaging, MO Domain

Row #	STUDYID	DOMAIN	USUBJID	MOSEQ	MOGRPID	MOTESTCD	MOTEST	MOORRES	MOORRESU	MOSTRESC	MOSTRESN	MOSTRESU
1	XYZ	MO	XYZ-AB-333-009	1	1	RETINAL SCAN	AREA	10.94	SQ CM	10.94	10.94	SQ CM

MOLOC	MOLAT	MOMETHOD	MOEVAL	MODTC	VISITNUM	VISIT
RETINA	RIGHT	RETINAL IMAGING	INVESTIGATOR	2022-10-19	1	SCREENING

Figure 13: Reference CDISC Implementation Guide.

Advantage of mapping imaging data using image analysis techniques is precision and accuracy for of dimensions and calculation of change from baseline of measurements. On the other side, there are some challenges related to scaling the images, image noise and consistent image perspective, image resolution and device calibration.

TELEHEALTH FOR EYE CARE

Digital images of the retina hold tremendous promise in remote patient monitoring in the current time. One of the first application of Tele-Ophthalmology was in 1987. With the use of a portable video fundoscope retinal blood vessels of astronauts were monitored in real time during space flights. With advancements in Artificial Intelligence, the ability to diagnose diseases will be augmented with machines learning algorithms.

CONCLUSION

In this paper we discussed the various measures that can be adopted to get maximum data related to a patient's eye condition for ophthalmology-related trials. Many classification algorithms may also be applied to classify diseased and normal retinal scans. Patients may be monitored in between visits; image segmentation and analysis methods may be used to calculate disease condition in scanned data. Medical image analysis is an important approach to detect many ophthalmic conditions including some of the most prevalent causes of blindness in the industrialized world that includes age-related macular degeneration, diabetic retinopathy, and glaucoma. Retinal disease detection with screening measures used in telemedicine is a cost-effective method that enable an easy-to-use, automated analyses of the images, and focused reporting of the results. With enhanced technology, automation, machine learning and artificial intelligence, there is greater possibility of achieving meaningful research outcomes and better treatments for vision.

REFERENCES

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16. “Telehealth Implementation in Retina Practices During COVID-19.” Retina Today, Bryn Mawr Communications, retinatoday.com/articles/2020-may-june/telehealth-implementation-in-retina-practices-during-covid-19.

IMAGE SOURCES:

1. How the eyes work. 2019. https://www.nei.nih.gov/learn-about-eye-health/healthy-vision/how-eyes-work
2. NEI-medialibrary-5261899.jpg. 2020. https://medialibrary.nei.nih.gov/media/3723
3. NEI-medialibrary-3315734.jpg. 2019. https://medialibrary.nei.nih.gov/ media/3497
4. NEI-medialibrary-6928570.png. 2019. https://medialibrary.nei.nih.gov/media/1804
5. NEI-medialibrary-1207347. 2019. https://medialibrary.nei.nih.gov/media/3556
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7. NEI-medialibrary-6983558.png. 2019. https://medialibrary.nei.nih.gov/media/3555
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ACKNOWLEDGMENTS

The author would like to thank Dr. Dinesh P. Mital, PHD, Professor- Rutgers University for reviewing the paper and providing valuable feedback.

RECOMMENDED READING

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