USING BOX-COUNTING DIMENSION TO CHARACTERIZE DIFFERENT STAGES OF DIABETIC RETINOPATHY

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INTRODUCTION

Diabetic Retinopathy:

Diabetic retinopathy is a disease affecting the retinal vessels of diabetes patients, characterized by the presence of microaneurysms, hard exudates, soft exudates, and hemorrhages, in order of increasing severity. The progression of diabetic retinopathy is divided into four stages, with the first two stages being *non-proliferative* and the final two being *proliferative*. In the proliferative stages, new fragile vessels form in a process called *neovascularization*.

Box-Counting Dimension:

The complexity of self-similar patterns (e.g. blood vessels, root patterns, lung bronchioles) may be measured using *fractal dimension*. Fractal dimension may be expressed as a function of self-similar copies and scale:

$$\boldsymbol{d = \frac{ln(N)}{ln(r)}}$$

This may be computed simply using the box-counting method, which involves enclosing the pattern in progressively smaller boxes and obtaining a ratio.

RATIONALE

Computers have increasingly been used to identify and diagnose diseases as an alternative to manual detection (e.g. breast cancer imaging). Technology may be used to decrease the probability of misdiagnosis by accurately analyzing parameters that are indicative of the disease. The box-counting method may be applied to images of retinas affected by diabetic retinopathy provided by the DIARETDB0 database. The DIARETDB0 database contains the ground truths of 130 color fundus images, with each image categorized into five groups (the four stages of diabetic retinopathy and one control group). The fractal dimensions of retinal vessels in each progressive stage may be compared to detect any significant difference. Furthermore, blood vessels exhibiting new growth, or neovascularization, may be analyzed for a significant increase compared to retinal vessels in the non-proliferative stages.

RESEARCH QUESTION / HYPOTHESES

Is there a significant difference in the box-counting dimensions of retinal vessels affected by diabetic retinopathy compared to those that are unaffected?

$\boldsymbol{H_0}$: There is no significant difference between the fractal dimensions of retinal vessels affected by diabetic retinopathy and the control group.

$\boldsymbol{H_A}$: There is a significant difference between the fractal dimensions of retinal vessels affected by diabetic retinopathy and the control group.

Is there a significant increase in the box-counting dimensions of retinal vessels exhibiting neovascularization compared to those in the non-proliferative stages?

$\boldsymbol{H_0}$: There is no significant increase in the fractal dimensions of retinal vessels exhibiting neovascularization.

$\boldsymbol{H_A}$: There is a significant increase between the fractal dimensions of the retinal vessels exhibiting neovascularization.

METHODOLOGY

The Box-Counting Method:

The box-counting method begins with enclosing a fractal pattern in a square box, which is taken to be unit length. It's divided into smaller boxes of length $\frac{1}{3}$, shown in Figure 1. **Magnification** is defined as the inverse of the box length, so in this case, it equals 3.

Note: In the diagrams below, boxes that aren't occupied by the fractal pattern are omitted. Boxes have been truncated in unoccupied areas by the pattern for the purpose of saving space.

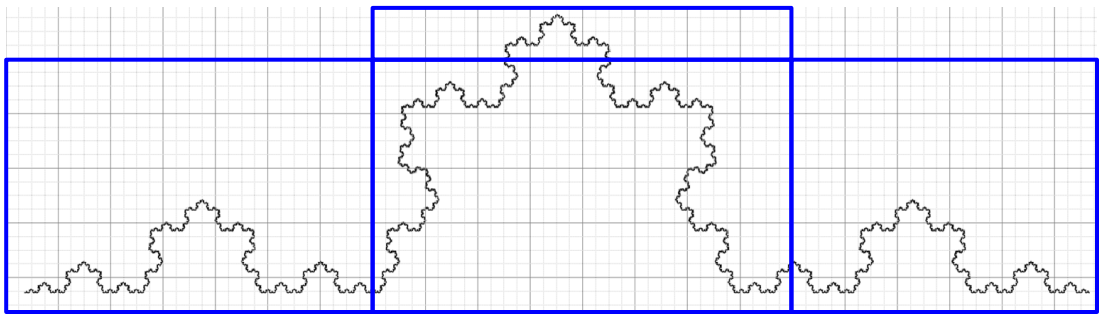


Figure 1. The fractal occupies 4 boxes of the grid.

The process is repeated with box sizes $\frac{1}{3}$ the size of the previous ones; they are therefore of magnification 9.

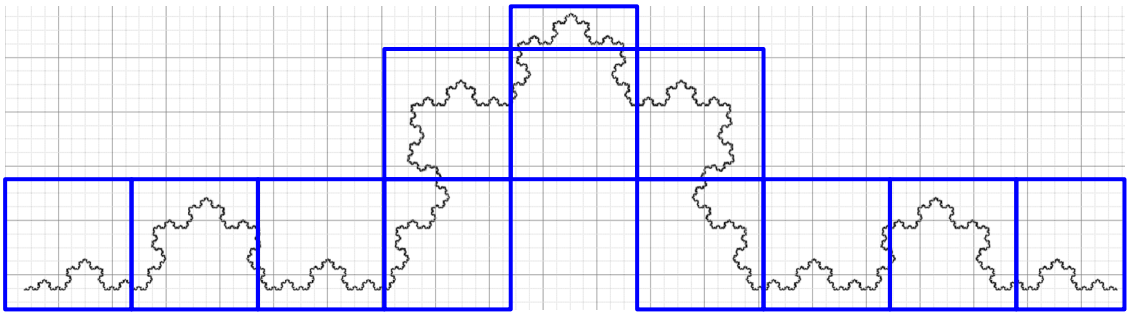


Figure 2. The fractal occupies 12 boxes of the grid.

This process is repeated once more at a magnification of 27:

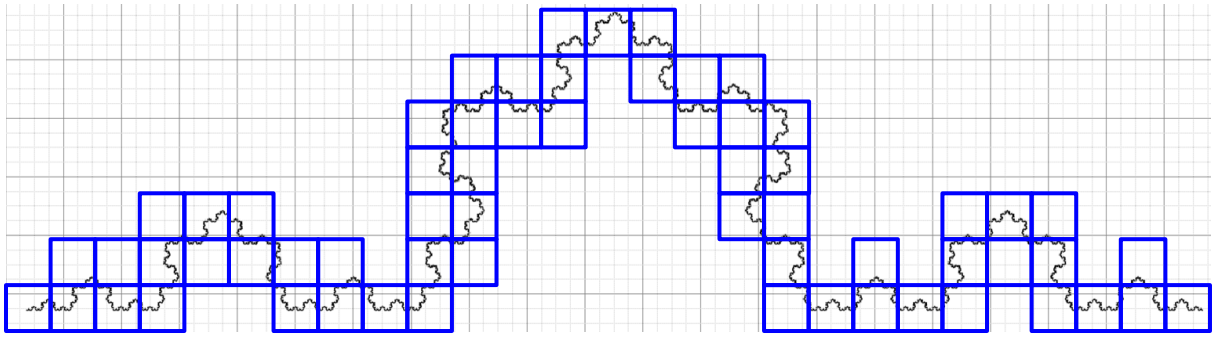


Figure 3. The fractal occupies 62 boxes of the grid.

The results from these three calculations are summarized in a data table.

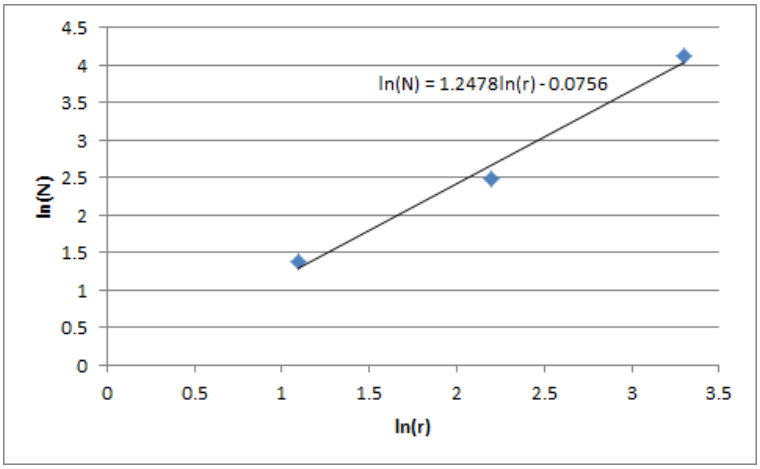
Table 1. Results of *Koch Curve* Box-Counting Analysis

Magnification	Number of Occupied Boxes (N)
3	4

9	12
27	62

From these results, we plot the points on a log-log graph with magnification on the horizontal axis and the number of occupied boxes on the vertical axis. The line of best fit is plotted, and the slope is equivalent to the fractal dimension.

Graph 1. Log-Log Graph Fitted with Linear Regression



The estimated fractal dimension of the Koch Curve is 1.25. As more iterations are completed, the value of the slope will approach $\frac{log(4)}{log(3)}$, approximated as 1.26.

This may be done automatically over 14 magnifications using the program FracLac. Each pattern must first be processed in the software ImageJ; this often requires background subtraction, thresholding, and noise elimination.

Procedure:

1. Divide 130 images into the following five groups as described by the ground truths of the DIARETDB0 database:

   Group 1: microaneurysms, hemorrhages, hard exudates

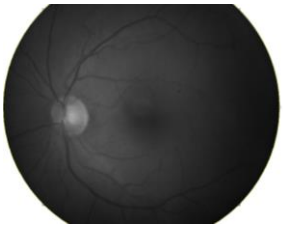
   Group 2: microaneurysms, hemorrhages, hard exudates, soft exudates

   Group 3: microaneurysms, hemorrhages, hard exudates, soft exudates, **neovascularization**

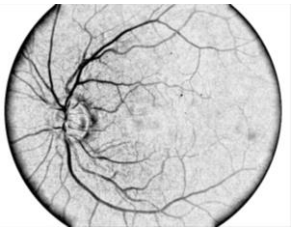
   Group 4: microaneurysms, hemorrhages, soft exudates, **neovascularization**

   Group 5: no symptoms (control)

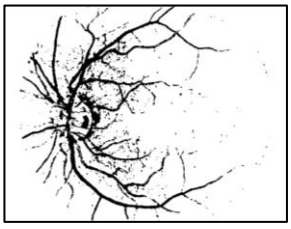
2. Using ImageJ, isolate the retinal vessel pattern using in the following technique:



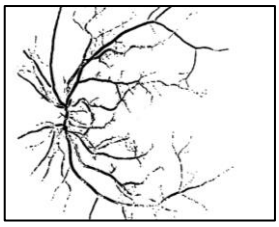
GRAYSCALE



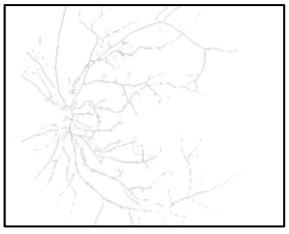
BACKGROUND SUBTRACTION
(5% CONTRAST)



BINARIZATION



NOISE ELIMINATION



SKELETONIZATION

3. Compute the box-counting dimension of selected images in each of the five groups using FracLac and find the mean.

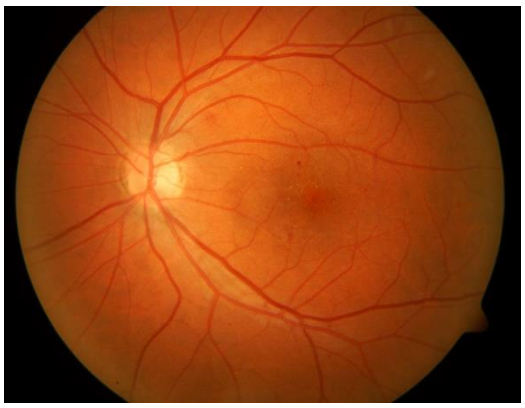
4. Determine the significance of the results using ANOVA and t-tests.

RESULTS

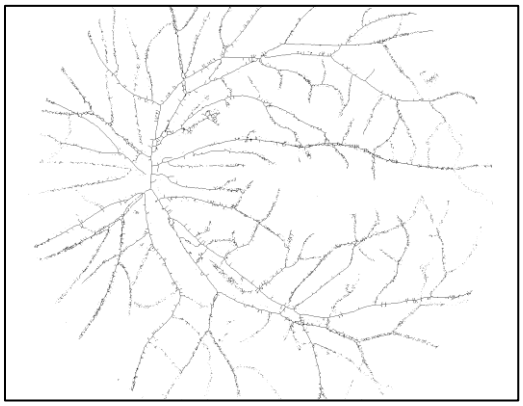
For each of the five groups, a select image's box-counting results are shown in addition to the dimensions of the three trials. The mean dimensions of Groups 1-4 are compared to the results of the control (Group 5) using a t-test and the p-value is recorded. The mean dimension of images from Groups 3 and 4 are compared with the mean dimension of those from Groups 1, 2, and 5 using a t-test; this determines any significant increase in the proliferative-stages exhibiting neovascularization compared to the non-proliferative stages.

Group 1:

IMAGE 6

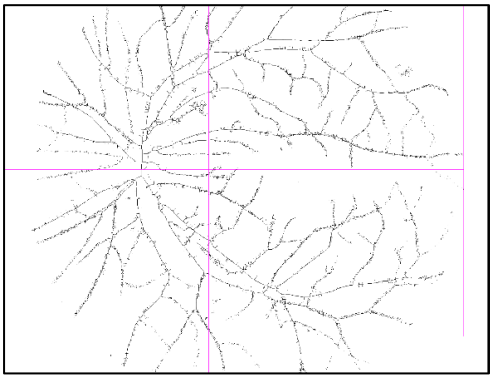


BEFORE

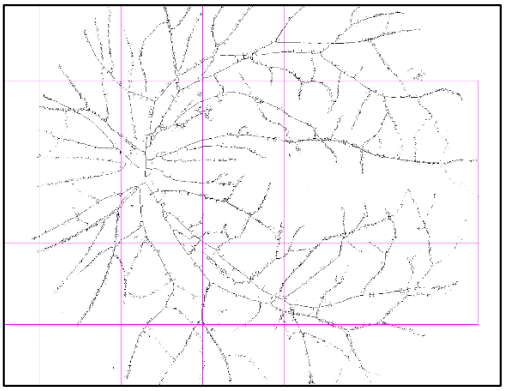


AFTER

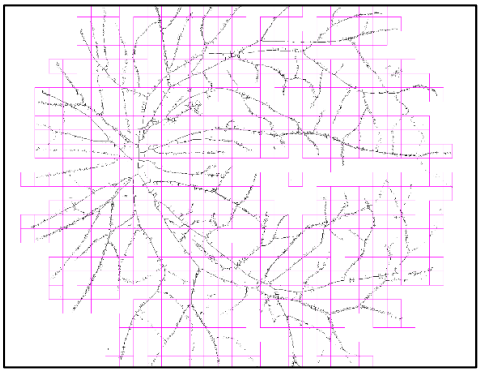
FracLac Results:



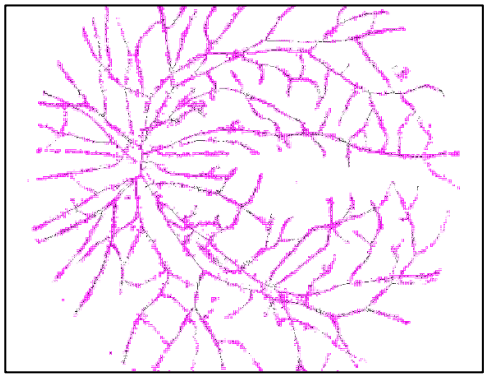
MAGNIFICATION 1



MAGNIFICATION 8



MAGNIFICATION 13



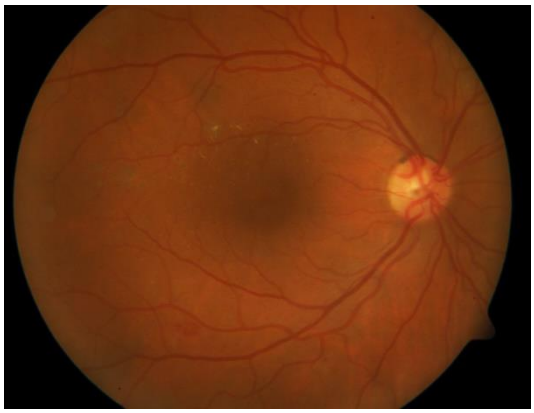
MAGNIFICATION 14

IMAGE	DIMENSION
IMAGE 6	1.597
IMAGE 21	1.5388
IMAGE 28	1.5532

$\bar{x} = 1.563$

Group 2:

IMAGE 11



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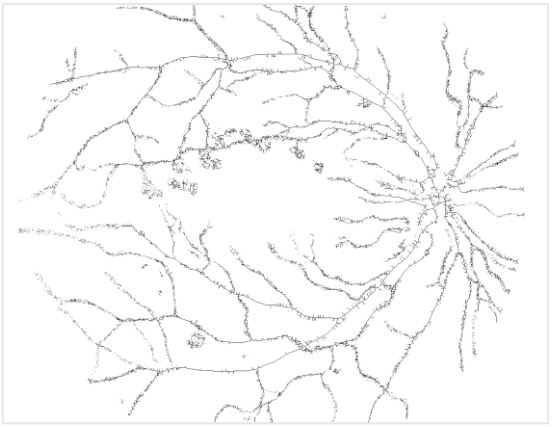
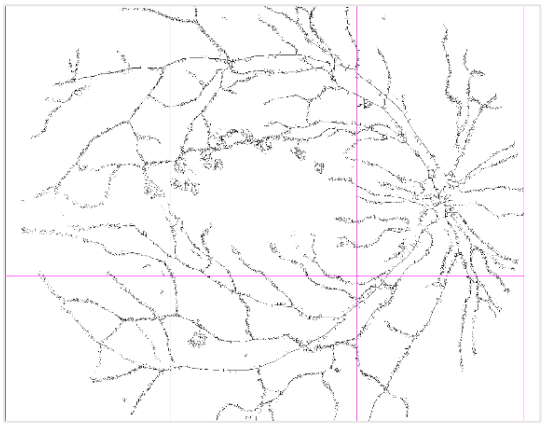
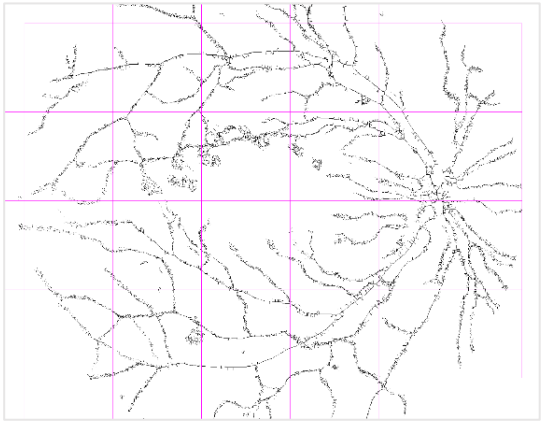


AFTER

FracLac Results:



MAGNIFICATION 1



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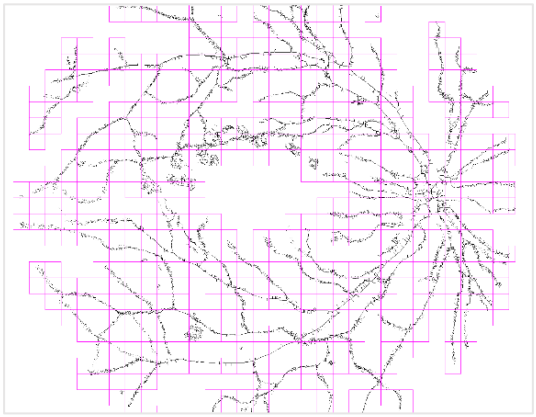
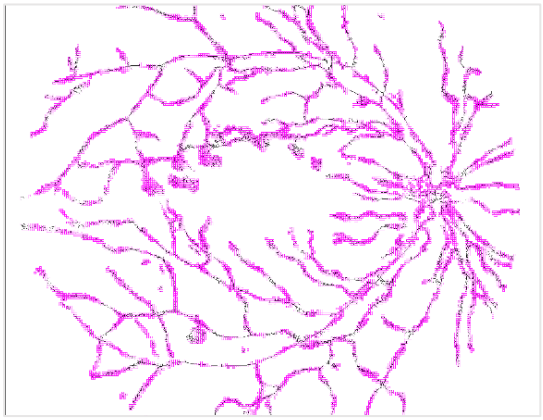


MAGNIFICATION 13



MAGNIFICATION 14

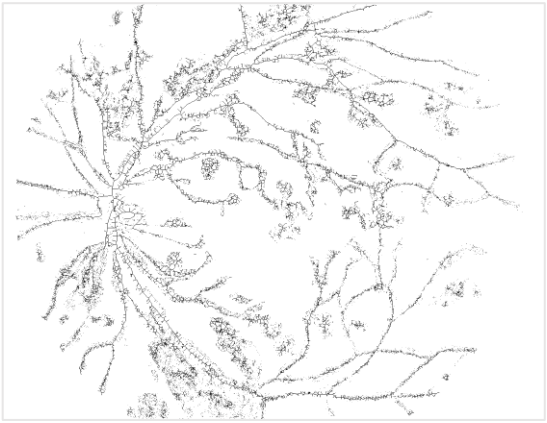
IMAGE	DIMENSION
IMAGE 9	1.5564
IMAGE 11	1.5923
IMAGE 74	1.5398

$\bar{x} = 1.56283$

Group 3:

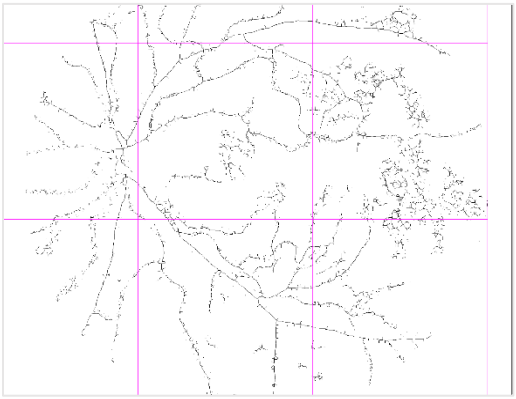
IMAGE 32

BEFORE

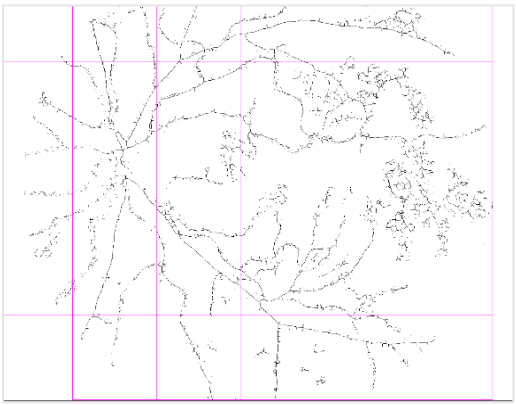


AFTER

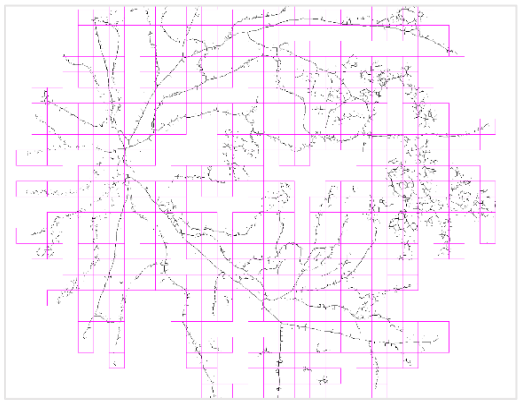
FracLac Results:



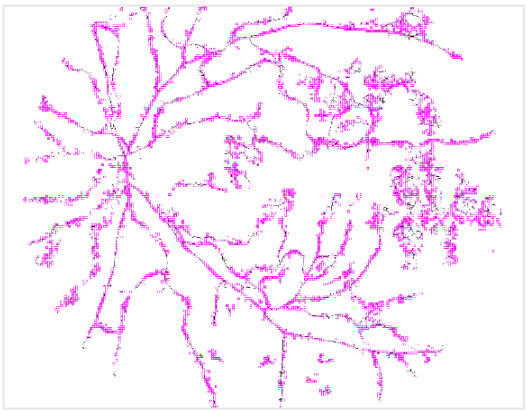
MAGNIFICATION 1



MAGNIFICATION 8



MAGNIFICATION 13



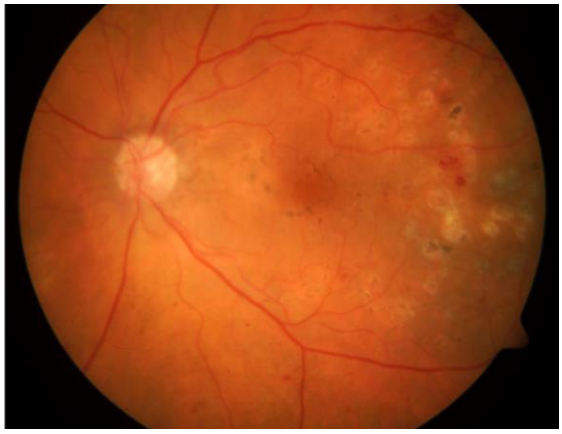
MAGNIFICATION 14

IMAGE	DIMENSION
IMAGE 31	1.5448
IMAGE 32	1.6642
IMAGE 43	1.5934

$\bar{x} = 1.6008$

Group 4:

IMAGE 37



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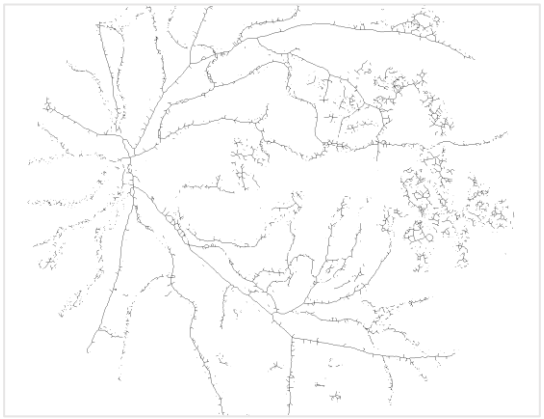
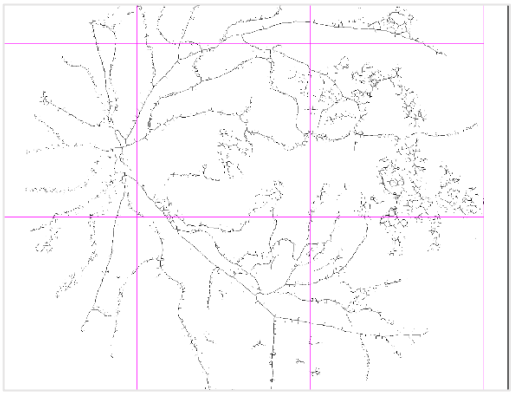
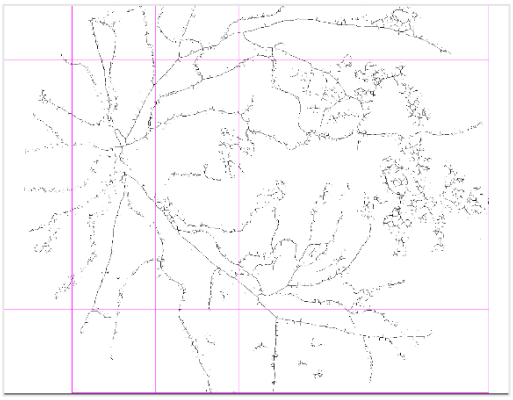


AFTER

FracLac Results:



MAGNIFICATION 1



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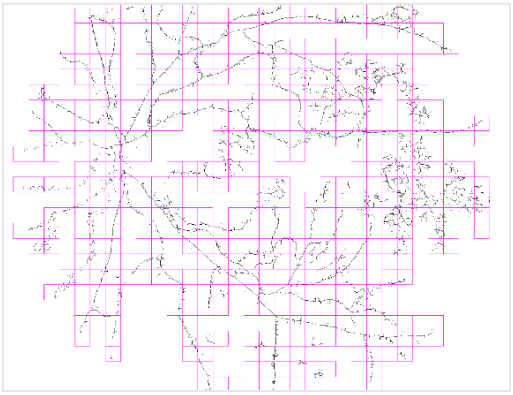

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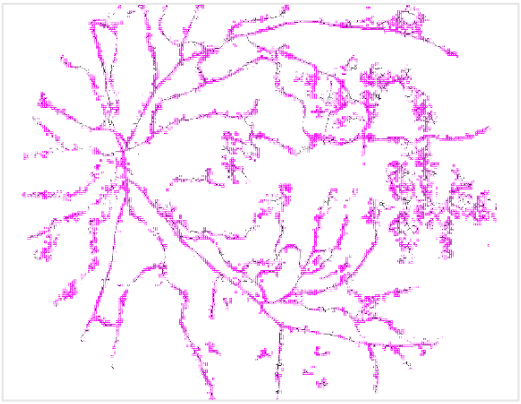


MAGNIFICATION 14

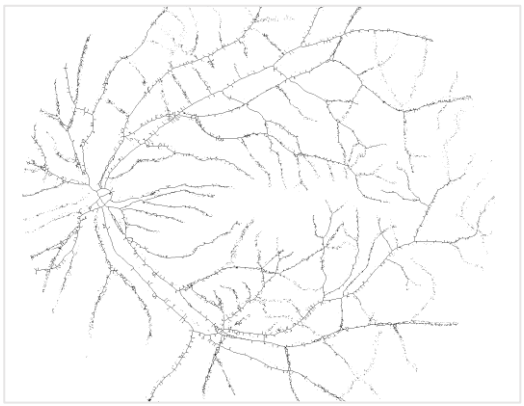
IMAGE	DIMENSION
IMAGE 37	1.5629
IMAGE 38	1.6319
IMAGE 45	1.6582

$$\bar{x} = 1.61767$$

Group 5:

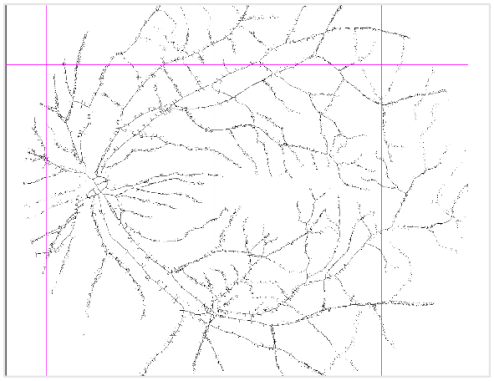
IMAGE 130

BEFORE

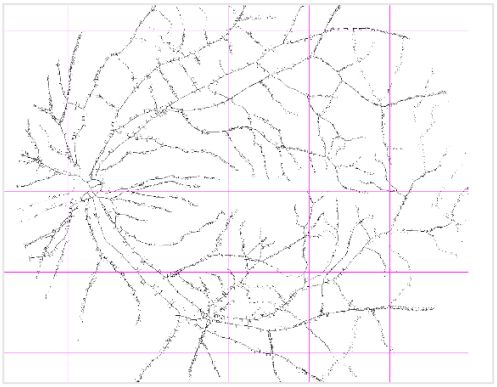


AFTER

FracLac Results:



MAGNIFICATION 1



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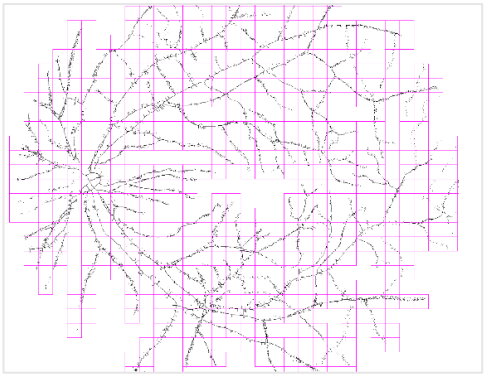
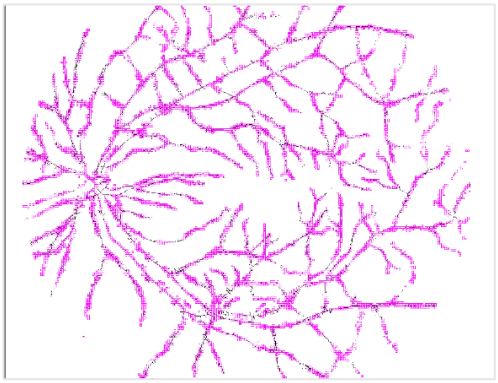


MAGNIFICATION 13



MAGNIFICATION 14

IMAGE	DIMENSION
IMAGE 82	1.538
IMAGE 123	1.5431
IMAGE 130	1.1.6112

$$\bar{x} = 1.5641$$

Statistical Analysis:

When matched with the control group, Groups 1, 2, 3, and 4 yielded p-values of 0.9721, 0.9666, 0.437, and 0.2229, respectively. An ANOVA test of all five groups results in a p-value of 0.2417. When the mean dimension of the images exhibiting neovascularization (Groups 3 and 4) were compared with that of the non-proliferative stages, a p-value of 0.0399 resulted.

DISCUSSION

Diabetic retinopathy is characterized by a series of abnormalities in the retinal vessels including microaneurysms, hard exudates, soft exudates, and hemorrhages. Proliferative diabetic retinopathy involves the growth of new vessels in the eye, called neovascularization. The box-counting method, especially when applied over many magnifications, is a simple yet effective tool for measuring the complexities of natural self-similar patterns, such as these blood vessels.

It was hypothesized that the fractal dimensions of retinal vessels with diabetic retinopathy may be different than the dimensions of the control group. In addition, it was hypothesized that the fractal dimensions of retinal vessels exhibiting neovascularization will be greater than those vessels in the non-proliferative stages due to an increased complexity.

CONCLUSIONS

There is no significant difference between the box-counting dimensions of each of the four stages of diabetic retinopathy compared to the control (t-tests). In addition, there is no significant difference between the dimensions of the five groups compared with each other (ANOVA).

However, there is a significant increase in the dimensions between retinal vessels exhibiting neovascularization and retinal vessels with non-proliferative diabetic retinopathy ($p = 0.0399$).

In order to yield more conclusive results in the future, a larger number of trials in each group will produce more accurate data averages. Another parameter, *lacunarity*, or the study of "empty space" and "gaps" in a self-similar pattern may be applied to these fundus images to further analyze diabetic retinopathy.

- *How can parameters like dimension and lacunarity be useful in analyzing morphogenetic systems and diagnosing other diseases?*

REFERENCES

- Audrey Karperien, Charles Sturt University. (n.d.). "FracLac for ImageJ". Retrieved from https://imagej.nih.gov/ij/plugins/fraclac/FLHelp/Introduction.htm

- DIARETDB0 - Standard Diabetic Retinopathy Database. (2007, May 30). Retrieved from https://www.it.lut.fi/project/imageret/diaretdb0/

- Fractal Analysis Reveals Reduced Complexity of Retinal Vessels in CADASIL. (2011, April 27). Retrieved from https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0019150